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PHILIP MORRIS BEHAVIORAL RESEARCH PROGRAM

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I. EXECUTIVE SUMMARY AND SHORT CHRONOLOGY OF CNS RESEARCH

Philip Morris had been interested since the 1960s in the benefits of smoking and why people smoke. William L. Dunn directed the programs that Philip Morris implemented to study these issues. For many years Philip Morris internal research focused on smokers' smoking behavior and attempted to measure how smoking affected behavior. Problems arose, however, in designing controlled studies that limited subject variability and experimental conditions.

During the 1960s and early 1970s Philip Morris was also funding outside research that examined the benefits of smoking as measured in animals, although some researchers also employed human subjects as well. Between 1969-1972 Ronald Hutchinson studied the effects of smoking on aggression in humans as measured by jaw clenching. He also studied the effects of nicotine administration on aggression in monkeys. Gary Berntson was funded between 1972 and 1981, and his consultancy with Philip Morris continued through 1983. Berntson's work also involved investigating the benefits of smoking by studying the effects of nicotine on aggression in cats. He also examined the pain-reducing properties of nicotine in rats and cats. The last area of Berntson's research involved the effect of nicotine on learning and memory in rats and humans.

Robert Waldbillig was also funded by Philip Morris to investigate the effect of nicotine on aggression in rats. He was funded between 1974 and 1976.

These areas of investigation supported Philip Morris' view that smoking provided certain benefits to smokers, but there was no indication that Philip Morris intended to use any of the research results in commercial product development.

However, in 1977, Philip Morris began developing a program to identify a behavior or phenomenon that was measurably altered by smoke and was implicated in the reinforcement of smoking. In 1977, the Behavioral Research Program was restructured to include three units: General Experimental Psychology, Electrophysiology, and Comparative Psychology. The Electrophysiology and Comparative Psychology units were concerned with measuring the central nervous system (CNS) effects of smoking and nicotine. Frank Gullotta was hired to lead the Electrophysiology Program and to develop programs investigating the electrical activity within the CNS and how it was affected by smoking. Philip Morris wished to use the knowledge obtained from this research in strengthening its capability to develop new and improved smoking products.

At least two projects stand out as efforts undertaken by Gullotta to develop data obtained from electrophysiological recordings to use in making new products. In one study Gullotta examined reports by some subjects that a high nicotine delivery cigarette seemed weak and a low nicotine delivery cigarette seemed strong. Gullotta recognized the commercial potential for developing cigarettes that appeared to produce the CNS effects of a high delivery cigarette by leading smokers to believe they were smoking a high delivery cigarette when they were actually smoking a low delivery cigarette.

Another project with stated commercial application was the development of the Olfactory Evoked Potential (OEP) recorded in response to olfactory stimuli. Gullotta and outside consultants attempted to differentiate flavor and odor stimuli in terms of amplitude, latency, and waveform morphology. This work was valuable to Philip Morris in its programs to develop flavors and Burley tobacco alternative and to reduce irritating factors in sidestream smoke.

At about the same time that the Electrophysiology Program was begun, Philip Morris began the Comparative Psychology Program under Carolyn Levy. The goal of this program was to understand the pharmacological effects of smoke by observing the effects of nicotine on behavior in animals. By 1979 the major objective of the animal behavior studies was to develop behavioral tests sensitive to the effects of nicotine and which could be used to screen nicotine analogues for CNS effects. In 1980, Philip Morris hired Victor DeNoble to use behavioral pharmacology techniques to investigate nicotine and nicotine analogues. Philip Morris undertook a Nicotine Program which included the coordinated activities of several Philip Morris programs such as chemistry, electrophysiology and behavioral pharmacology. The Nicotine Program's goals were to develop nicotine analogues that had desirable CNS effects without the undesirable peripheral nervous system effects. This goal had commercial potential of making new products.

In conjunction with Philip Morris' in-house Nicotine Program, Philip Morris also worked with outside researchers to aid its program. In 1979 Philip Morris funded research by Leo Abood to isolate and characterize nicotine receptors in rat brain. He was also consulted for his expertise in helping Philip Morris develop the prostration syndrome bioassay in its own research program. Abood was also contracted to test proprietary compounds developed at Philip Morris. In 1981 Philip Morris contracted with John Egle to test nicotine analogues for peripheral nervous system effects.

For reasons never stated in any internal documents, Philip Morris cancelled the Nicotine Program in spring 1984. The decision to cancel the program may have been the result of outside counsel's legal advice.

Resources. Many Philip Morris internal documents were used to prepare this memorandum. The document identification number was cited along with the document's production history. The history stated whether the document had been produced, taken, placed on an exhibit list, or deemed privileged. The reference to "exhibit" following a case name indicated that the document was listed on the plaintiff's pre-trial exhibit list. It was not necessarily a trial exhibit. The same designation applied to a document described as "defendant's exhibit" meant the document was listed on the defendant's pre-trial exhibit list.

Many Shook, Hardy & Bacon memoranda were used to prepare this memorandum. For more information on a particular researcher's work, see the following:

Abood	Philip Morris Support for Leo Abood, July 1, 1986, Theresa R. Smith
Berntson	Gary G. Berntson; Philip Morris Sponsored Research, September 16, 1987, Nancy J. Anderson
DeNoble	Dr. Victor J. DeNoble, August 30, 1988, Kathryn L. Jones
Egle	Philip Morris Sponsored Research Performed by John L. Egle, Jr., Medical College of Virginia, July 10, 1987, Orville L. Barnett
Hutchinson	Ronald R. Hutchinson, September 8, 1987, Anthony J. Miella and Mary D. Sawyer
Waldbillig	Philip Morris Sponsored Research at Rockefeller University, September 22, 1987, Nancy J. Anderson and Mark Peterle.

Short Chronology.

Date	Event
1969	Hutchinson funded
1972	Berntson funded
	Hutchinson funding ceased
1974	Waldbillig funded
1975	Levy hired

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1977	Berntson hired as consultant
	Gullotta hired
	Electrophysiology and comparative psychology programs initiated
	Waldbillig funding terminated
1979	Abood funded
1980	DeNoble hired
1981	Egle funded
	Berntson research terminated
1984	Egle funding terminated
	DeNoble terminated
	Berntson consultancy lapses
	Abood funding terminated

II. INTRODUCTION

William L. Dunn directed the Philip Morris Behavioral Research Program. In 1969, Dunn's outline for the Annual Report indicated that the program was called Consumer Psychology at that time. This document demonstrated that Philip Morris had not yet begun CNS research, but was focusing on research designed to investigate smokers' smoking behavior in more general terms. A brief mention was made of a "rat project" with a goal of producing smoking animals in an effort to determine whether nicotine dependency could be produced in different strains of rats. No other details were provided. [1000344589-4596, Cipollone taken, all redactions removed]

By 1974, documents indicated that the program's name had changed to Smoker Psychology/Behavioral Research Program. The research conducted in this time period was designed to test several hypotheses focusing on how smoking could affect behavior. For instance, Philip Morris tested whether smoking improved efficiency or influenced aggression, learning or emotional arousal. Other studies tested whether changes in smoke deliveries affected puff patterns. These types of projects were carried out for several more years until 1977.

On December 1, 1976, Dunn outlined in the Plans and Objectives for 1977 a reorganization of the Behavioral Research Laboratory to include three units. These were the General Experimental Psychology Unit, the Electrophysiology Unit and the Comparative Psychology Unit. [1003293166-3171, Cipollone exhibit] Only research conducted in the Electrophysiology Unit and the Comparative Psychology Unit is within the scope of this memorandum. The General Experimental Psychology Unit will not be discussed here.

III. IN-HOUSE RESEARCH PROGRAMS

A. Electrophysiology Program (Charge 1620)

1. Definition of Terms

In the discussion of the Electrophysiology Program, many technical terms were used. In an effort to aid understanding of this work, the following definitions are provided. All definitions were obtained from a Philip Morris document. [820705, 1003179058-9107 (p. 9060-9061), not produced]

AMPLITUDE - EVOKED POTENTIAL - The height of some component of the multiphasic EP waveform, measured either from a zero baseline, or with respect to another component.

AUDITORY PATHWAY - peripheral, pontomedullary, pontine, midbrain- In ascending order, the lower portion of the auditory pathway, extending from the inner ear and auditory nerve to the thalamus.

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP) - Far-field auditory EP which is generated by neural elements located (principally) in the brainstem. It consists of seven peaks which occur within 10.0 msec after acoustic stimulation. Optimal stimuli are rarefaction clicks occurring between 10 and 30 clicks/sec.

CENTRAL NERVOUS SYSTEM (CNS) - The brain and spinal cord.

COMPONENT/PEAK - EVOKED POTENTIAL - One wave of the multiphasic EP waveform. Usually identified in terms of polarity (P or N) and either its normal latency or its ordinal relationship to other peaks (e.g., P_{100} or P_1).

EEG POWER SPECTRUM - Time series (fast fourier) analysis of the ongoing EEG. It yields numerical data about the amount and/or percent of energy at the various frequencies (i.e., 0 - 40 Hz) contained within the EEG.

ELECTROENCEPHALOGRAM (EEG) - A record of the continuing electrical activity of the brain. It is usually recorded from the scalp via gold or silver electrodes positioned over the brain areas under study.

ELECTROTRIGEMINOGRAM (ETG) - A record reflecting the depolarization of the free nerve endings of the trigeminal nerve. In this case, the ETG refers to the depolarization potential recorded from the inner, lateral surface of the human nose.

EVOKED POTENTIAL (EP) - The electrical response of the brain to the onset of a sensory stimulus, such as a light, tone, odor, etc. In general EPs are small multiphasic waveforms which must be signal averaged to extract them from the ongoing (and much larger) EEG.

FAR-FIELD RESPONSE - EVOKED POTENTIAL - A response which is recorded distal to its neural generators. For example, the BAEP is a far-field response because, although it is recorded at the cortex, its neural generators are located in the brainstem. (The PREP is a near-field response, since its neural generators are in visual cortex).

FEELING FACTORS - IN CIGARETTE SMOKING - The spicy or peppery quality of smoke. Feeling factors are thought to be mediated by stimulation of the trigeminal nerve.

LATENCY - EVOKED POTENTIAL - The time from stimulus onset to the occurrence of some component (peak) of the EP waveform.

N_1-PREP - The first negative component of the PREP. Its normal latency is approximately 70.0 ± 3.0 msec.

OLFACTORY EVOKED POTENTIAL (OEP) - The cortically recorded response of the olfactory system to the onset of an odorant.

PATTERN REVERSAL EVOKED POTENTIAL (PREP) - The cortically recorded response of the visual system to a shifting pattern (usually a checkerboard).

P_{100}, P_1 - PREP - The primary positive component of the PREP. Its normal latency is 100.0 ± 5.0 msec.

RAREFACTION CLICK - IN BAEP RECORDING - A click produced by the inward movement of the diaphragm of an earphone. Rarefaction clicks are the preferred BAEP stimuli since they produce good peak resolutions.

SIGNAL AVERAGING - EVOKED POTENTIAL - The process by which an evoked potential is extracted from the ongoing EEG. Since the evoked potential is time-locked to stimulus presentation, it can be computer summated. The ongoing EEG is random with respect to stimulus presentation and is averaged to zero. The number of stimulus presentations necessary to record a clear evoked potential varies with the signal (evoked potential) to noise (EEG) ratio.

TRIGEMINAL NERVE - The fifth cranial nerve, widely distributed throughout the head and neck.

2. Objectives of the Electrophysiology Program

Beginning in about 1974, the Behavioral Research Program's stated goals for several years remained the same:

I. To learn more about why people smoke.
II. To learn more about how people smoke.
III. To identify what people want to smoke.
[1003293183-3185, Cipollone taken; 1003293177-3182, Cipollone taken; 1003293172-3176, Cipollone taken]

This research continued in an apparently general way until 1977 when another goal was introduced:

IV. To identify a quantifiable behavior or physiological phenomenon which meets these two criteria:

a. Is measurably altered by smoke inhalation.

b. Can be conceptually construed to be implicated in the reinforcement of the smoking act. [1003293166-3171, Cipollone exhibit]

To achieve its goals as outlined above in IV, Philip Morris recruited Frank Gullotta to join Philip Morris in 1977 and to set up the electroencephalography (EEG) laboratory. His task was to monitor the electroneurological events underlying psychological states. The program's goal was "to conduct research on human smoking wherein the dependent variable is an electronic signal mimicking a human physiological event. Since it is widely believed that the reinforcement of cigarette smoking occurs within the central nervous system, electrical activity from within that system will be the principle source of data." [1003293166-3171, Cipollone exhibit, emphasis added]

It was not until the Plans and Objectives for 1979 were written that any opportunity for commercial application of this research was mentioned. Dunn wrote that the program's objectives were to understand the reward a smoker gets, to understand the psychophysiological action of the reward, and to relate the reward to the constituents in smoke. This knowledge would "strengthen Philip Morris R&D capability in developing new and improved smoking products." [1003293151-3159, Cipollone taken]

In the Plans and Objectives for 1981, Dunn outlined the individual programs in the Behavioral Research Program and stated that each "is but a varied attack upon the overall objective of the Behavioral Research Program to contribute useful knowledge about the response of the smoker to the cigarette and its smoke. The results may prove useful in developing a new product, or improving an existing product, or in the defense of the company from legislative or litigative harassment." [1003293130-3137, Cipollone taken, defendant's exhibit]

The specific objectives for Gullotta's electrophysiology program remained the same in 1981 as in previous years: to determine how smoking affected brain electrical activity and to identify the neural elements which mediated smoking's reinforcing actions. [1003293130-3137, Cipollone taken, defendant's exhibit] There follows a discussion of the major projects conducted by Gullotta in pursuit of the program's objectives.

3. Discontinued Studies

The following studies were discussed by Dunn in the Plans and Objectives for 1977 before Gullotta joined Philip Morris. [1003293166-3171, Cipollone exhibit] Gullotta pursued these studies, but they were evidently quickly abandoned as no further discussion was found in the documents.

a. Alpha Wave Habituation

By 1976, Philip Morris was aware of other scientists' research demonstrating that smokers adapted more rapidly to intrusive auditory stimulation than did deprived smokers. Philip Morris was interested in this research to determine whether smokers smoked to insulate themselves from disruptions. Dunn wrote that Philip Morris was interested in the possibility that these research results might be translated into an index to identify and assess the "critical components of smoke." [1003293166-3171, Cipollone exhibit] This reference to Philip Morris' interest in "critical compounds" tacitly implied that the critical compounds could be manipulated in the development of new products.

Although it appeared that Gullotta did not pursue this line of research once he joined Philip Morris, he did plan to measure alpha brain wave frequencies and to observe changes associated with cigarette smoking. Gullotta planned to use cigarettes identical in all variables except nicotine content. [1003293160-3165, Cipollone taken] No further information was found.

b. Contingent Negative Variation (CNV)

By late 1976, Philip Morris was aware of other scientists' research on CNV, a small prolonged change in the brain's electrical potential associated with mental processes reflecting mental alertness. In the Plans and Objectives for 1977, Dunn wrote that Philip Morris was interested in learning more about this phenomenon and the reports that CNV was modifiable by smoke inhalation. Dunn thought that the measure had potential as an index of the pharmacological response to smoke. [1003293166-3171, Cipollone exhibit] Gullotta planned to continue this project in 1978; however, he acknowledged that some subjects demonstrated an increase in magnitude of CNV while smoking, while other subjects demonstrated a decrease. [1003293160-3165, Cipollone taken] No further information was found.

4. VEP

This was Gullotta's first brain research study assessing the effects of smoking on electrical brain events in response to visual stimulation by a flash of light. In his first Annual Report covering the period July 1977-June 1978, Gullotta reported that smoking's effect on the Visual Evoked Potential (VEP), one aspect of the gross EEG, was not clear-cut. There was no effect on the early components of the VEP (representing sensory processing), but there appeared to be an enhancing effect on the late and after-discharge components of the VEP. Gullotta planned to replicate previously conducted, but inadequately controlled studies. [1000369449-9495, Cipollone taken]

Repeat experiments regarding the first VEP study did not show the same results. Gullotta was unable to resolve the differences in results; however, he pursued this research, but changed some of the methods. [1000385482-5522, Cipollone exhibit] The follow-up studies are discussed below in section 7, PREP.

5. Smoking and the EEG

In the Plans and Objectives for 1979, Gullotta proposed replicating studies examining the effect of smoking and nicotine administration on EEG activation. [1003293151-3159, Cipollone taken] Gullotta recorded ongoing EEG activity and began the process of developing a spectral analysis program to allow him to perform analyses of ongoing EEG data from a number of brain loci under varying conditions of smoking and smoke deprivation. [1003293138-3144, Cipollone taken] Because of technical difficulties this project was not started until 1981. [1003293130-3137, Cipollone taken, defend.'s exhibit] No more information on this study was found.

6. AEP

Gullotta began studies of the Auditory Evoked Potential (AEP) in late 1979. Previous results had shown increases in the amplitude of the late components of VEP. Gullotta hypothesized that smoking and nicotine administration produced a generalized stimulant effect on the CNS. He predicted that all Sensory Evoked Potentials would be enhanced following smoking or nicotine administration. On the other hand, if Gullotta found a depressing effect on AEPs, he would conclude that smoking had a selective effect on the CNS, rather than a generalized enhancing effect. [1003293138-3144, Cipollone taken] He found that AEPs were not enhanced, and he therefore concluded that smoking had a specific and selective rather than a general effect on the CNS and that not all sensory systems were equally influenced by smoking. He speculated that it was possible that smoking may have different effects on the various neural systems which mediated behavior. His results did not support the idea that smoking had an overall arousal effect on the smoker. [1000385482-5522, Cipollone exhibit]

7. PREP

A study on Pattern Reversal Evoked Potential was begun in 1980. Gullotta had previously reported that smoking increased the amplitude of the late components of the VEP to flash stimulation. However, flash stimulation activated nonspecific brain structures as well as specific structures such as the primary visual cortex. To correct this problem, Gullotta employed another type of VEP called PREP by stimulating subjects with a checkerboard pattern to activate primarily visual structures and to study the effects on visual information processing. [1003293130-3137, Cipollone taken, defend.'s exhibit] This method was very reliable, and Gullotta conducted more studies, as described below.

a. PREP: Dose/Response, Deprivation and Time Factors

Gullotta had previously reported that smoking altered the Pattern Reversal Evoked Potential (PREP). He continued his studies to determine whether factors such as nicotine dose, smoke deprivation or time interval would also effect the PREP. He reported that high delivery cigarettes affected amplitude and latency; medium delivery cigarettes did not affect amplitude, but shortened latency only following deprivation; and low delivery cigarettes affected neither amplitude nor latency, irrespective of deprivation. [820705, 1003179058-9107, not produced]

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b. Repetitive Smoking and PREP

This study was a continuation of previous studies finding that high delivery nicotine cigarettes affected the PREP whether or not subjects were deprived and that medium delivery nicotine cigarettes altered PREP only under conditions of smoke deprivation. Low delivery cigarettes produced no changes. Gullotta wondered whether it was possible to mimic the effects produced by the higher nicotine delivery cigarettes by having subjects smoke several of the lower delivery cigarettes. Although Gullotta did not state so in his Annual Report, this study could have had commercial implications in that Philip Morris was attempting to determine whether a low delivery cigarette could produce CNS effects similar to those of a high nicotine delivery cigarette that a smoker would find more "satisfying." Philip Morris would be interested in the product development opportunities of this possibility. He reported that smoking three medium cigarettes resulted in a reduction in latency similar to that resulting from smoking one high delivery cigarette. However, no changes in amplitude were noted. No significant effects were obtained by smoking three low delivery cigarettes. Gullotta concluded that a threshold might exist between the low and medium delivery cigarettes. [820705, 1003179058-9107, not produced]

c. Perception and Smoking Effects on PREP

A very interesting study, and one with commercial application, was a result of observations that subjects might comment that a high delivery cigarette was weak or vice versa. Gullotta wanted to study the influences of the pharmacological and perceptual factors of smoking on PREP. Based on previous findings that smoking produced PREP latency shifts, Gullotta hypothesized that PREP latency shifts would reflect pharmacological factors, while amplitude effects would reflect both pharmacological and perceptual factors.

As predicted, results showed that latency changes reflected the nicotine delivery of the cigarette smoked. The amplitude measured the interactive effects of nicotine delivery and the smoker's perception. Results showed that either smoking a strong cigarette or smoking a weak cigarette that was perceived as strong produced amplitude reduction. The critical point regarding this study, although just a preliminary one, was that Gullotta stated that it may be possible:

> to alter CNS responses to cigarettes by altering how people perceive them. For example, we might be able to produce the CNS effects of high delivery cigarettes by leading subjects

to believe they were smoking high nicotine cigarettes when they were actually smoking low nicotine cigarettes. Experiments of this type might have important implications for the marketing of low delivery cigarettes. [820705, 1003179058-9107 (p. 9083), not produced, emphasis added]

d. Analysis of Market-Brand Cigarettes Using PREP

Gullotta used the PREP to analyze the use of market-brand cigarettes. He was interested in comparing the effects on the PREP of both market-brand cigarettes and experimental cigarettes. He tested a number of commercial cigarettes with different nicotine deliveries to assess how well the data fit his hypothetical curves derived from previous studies. He found that under controlled smoking conditions, the latency shifted in a manner approximating what would be predicted on the basis of FTC nicotine deliveries. In contrast, however, he reported that Barclay cigarettes produced results at odds with what would be predicted on the basis of FTC nicotine deliveries. The results indicated that Barclay's actual delivery was higher than its FTC rating. Under ad lib Barclay smoking conditions, the latency shifts were slightly greater than those in controlled smoking conditions for Barclay. Gullotta interpreted his results to mean that smokers could achieve CNS effects with ultra-low delivery cigarettes comparable to those obtained with high delivery cigarettes. These data contradicted the common belief that people could not smoke ultra-low delivery cigarettes for nicotine. He suggested the possibility that smokers might modify their smoking behavior in order to obtain some optimal CNS levels of nicotine. He concluded that, "the PREP may be an extremely sensitive alternative method for addressing the actual nicotine deliveries of current and new brands, and for determining how smokers modify their smoking behavior in response to different cigarettes and brand modifications." [820705, 1003179058-9107, not produced] Gullotta continued this study into 1983, but results were not reported. [830629, 1003186659-6717, not produced]

e. Return to Baseline

In 1983, Gullotta reported the results of a study examining how long CNS effects endured following smoking a single cigarette. This work was related to Philip Morris' interest in the timing and rate at which cigarettes were smoked to determine whether CNS effects affected smoking rate. Smoking produced a significant decrease in PREP latencies which lasted ten minutes after smoking. Latencies did not return to pre-smoking baseline levels until 60 minutes after smoking. Gullotta concluded that the decreased latencies were short-lived, and that, theoretically,

smokers may be smoking, in part, in response to CNS cues. [830629, 1003186659-6717, not produced]

8. BAEP

Gullotta also examined the effects of smoking on Brainstem Auditory Evoked Potentials (BAEP). An advantage of these brainstem potentials relative to more traditional forms of recording was that the nerves associated with the BAEP components were better known. For instance, Peak I was due to VIIIth nerve activity, etc. [1003293130-31337, Cipollone taken, defend.'s exhibit] Gullotta believed that BAEPs would be sensitive to smoking based on observations that smoking after long-term abstention produced clinical signs of brainstem dysfunction such as vertigo and ataxia and that novice smokers reported nausea, vertigo, and palpitations upon smoking. These were clinical symptoms of brainstem involvement which Gullotta wished to know whether or not were reflected in the BAEP. He also wanted to investigate whether BAEP amplitude depression could be related to the clinical signs of brainstem dysfunction as seen in novice smokers. [1000385482-5522, Cipollone exhibit]

Gullotta found that smoking did not decrease BAEP amplitudes. Amplitudes remained stable irrespective of smoking and/or deprivation despite the fact that in approximately 30% of the time subjects reported nausea after smoking a high delivery cigarette following deprivation. He concluded that the BAEP was not an effective means to assess smoke-induced signs of brainstem involvement. [820705, 1003179058-9107, not produced]

9. OEP

In 1982, Gullotta undertook a program with definite commercial application. He began a joint program with Dr. Ikeda of the Flavor Development Department and with German scientists to quantify how subjects responded to olfactory stimuli. PM had great interest in developing tobacco flavorings, investigating Burley tobacco alternatives, and reducing irritability factors in sidestream smoke; therefore, Gullotta developed an Olfactory Evoked Potential (OEP) program to explore the relationships among chemical properties of an odorant, the OEP, and the subjective response. Doctor Ikeda suggested that trigeminal nerve stimulants are often classed as irritating, but that small amounts of trigeminal nerve stimulation may create a desirable feeling factor associated with cigarette smoke. Gullotta engaged the German scientists to screen common flavorants to assess whether odorants with trigeminal properties had distinctive OEP characteristics. They found that odorants that stimulated the trigeminal nerve produced OEPs that were larger, more distinct and had shorter latency than those that did not. Philip Morris was planning to establish a laboratory to

begin recordings at R&D. Gullotta began recording OEPs using CO_2, limonene, and a combination of both. He made plans to obtain OEP profiles for odorants of interest to the Flavor Department. They were to consider identifying and eliminating irritative factors in sidestream smoke. Another goal was to find acceptable Burley tobacco substitutes. [820705, 1003179058-9107, not produced]

In 1982-1983, Gullotta continued research on olfactory and trigeminal EPs. The objectives of the program were to develop and use new techniques to quantify physiological responses to smoke constituents and tobacco flavorings. A study was carried out with exposure to limonene (an odorant), methylsalicylate (a trigeminal stimulant) and combinations of these with CO_2. The stimuli were differentiated in terms of latency, amplitude and waveform morphology. Flavor research was conducted by outside German consultants with vanillin, CO_2, menthol and a combination of vanillin and CO_2. [830629, 10036659-6717, not produced] This was the last report of Gullotta's program found. No further information was available.

B. Comparative Psychology/Behavioral Pharmacology Programs (Charge 1610)

1. Definition of Terms

In the discussion below of Carolyn Levy's and Victor DeNoble's work, many technical terms were frequently used. In an effort to aid understanding of this work, the following definitions are provided. All definitions were obtained from documents authored by DeNoble.

ADDICTION - "Addiction" must meet the following criteria:
(1) disruption in on-going behavior occurs when addictive drugs are self-administered;
(2) behavioral changes occur upon the termination of drug administration;
(3) "addictive" drugs are preferred to more conventional reinforcers (i.e., food, water, saccharin, etc.). [800723, 1003060621, Cipollone produced; Rothgeb produced]

PHYSICAL DEPENDENCE - Characterized by an abstinence syndrome when the availability of various psychoactive drugs is abruptly terminated or when an antagonist is administered. This can be quantified and qualified by changes in schedule controlled behavior. [810824, 1002973585, 1002973586-3615 (p. 3612) Cipollone taken; Rothgeb produced; Shires taken; 1000040405-0410, Cipollone taken; Rothgeb produced; Shires taken]

REINFORCER - A compound or event that: (1) an organism works to make available, and (2) that event or compound requires additional work. Many chemical compounds and physical stimuli can be self-administered (i.e., food, water, heat, saccharin) and are therefore considered reinforcers. [1003186527-6530 Rothgeb taken; Shires taken]

SELF-ADMINISTRATION - Technique used to determine the reinforcing properties of a compound.

TOLERANCE - (1) Metabolic - (also referred to as pharmacological) develops as a result of physiological changes due to the presence of the active agent, thus decreasing the effective concentration. Specifically, it may be caused by the following -

(a) result of pharmacokinetic factors which alter the effective concentration of the active agent at the receptor. These factors include: altered absorption, distribution, metabolic or elimination mechanisms.

(b) a decreased sensitivity of the receptor even though the concentration of the active agent remains the same. [1003060442, 1003060443-0503, Rothgeb produced]

(2) Behavioral - a diminished behavioral effect of a compound with repeated exposure to that compound without the inducement of metabolic tolerance. [1000040445-0451 Cipollone produced; Rothgeb produced]

WITHDRAWAL SYNDROME - Occurs upon termination of chronic drug administrations (i.e., ethanol, barbiturates, opiates, and psychomotor stimulants). The withdrawal syndrome can be measured as changes in schedule-controlled behavior. [1000040398-0401, Cipollone produced; Rothgeb produced; 1003060566, 1003060567-0598, Cipollone produced; Rothgeb produced; 1003175753, Rothgeb taken; Shires taken; 1003175754-5785, Rothgeb taken; Shires taken]

2. Objectives of Behavioral Pharmacology Program

The Comparative Psychology Program was initiated in 1977 under the direction of Carolyn Levy. The goal of this program was to conduct research on human smoking on the premise that if human smoking behavior was a function of the pharmacological effects of some component(s) of smoke, then the mechanisms supporting the behavior could be studied through the observation of the immediate, or short-term effects of the smoke component(s) upon the behavior of sub-human species. It was planned to use small rodents as subjects. [1003293166-3171, Cipollone taken, exhibit]

By 1979 Philip Morris' programs were really taking shape. The major objective of the animal behavior studies was to develop behavioral tests which were sensitive to the effects of nicotine

and which could be used to screen nicotine analogues for CNS activities. The studies planned were nicotine discrimination, tail flick (measuring analgesic properties), monitoring motor activity, prostration syndrome, nicotine self-administration, and rat EEG. [1003293218-3224, Cipollone exhibit, defend.'s exhibit; 1003293151-3159, Cipollone taken]

The 1980 Plans and Objectives for the Behavioral Research Program outlined the programs for the Comparative Psychology program. Carolyn Levy was transferring to Philip Morris New York and her program was turned over to her replacement, Dr. Victor DeNoble. The two major objectives were: (1) to develop and use animal behavior tests to screen nicotine analogues and (2) to learn more about the reinforcing properties of nicotine. [1003293138-3144, Cipollone taken]

The possible commercial application of this research was evident in Osdene's statement that the "major goal of the Nicotine Program is to develop nicotine analogues which will have desirable effects on the central nervous system (CNS) without the undesirable effects of nicotine on the peripheral nervous system." [Redacted in Rothgeb] The Nicotine Program relied upon several other programs to accomplish this goal, including investigations of the chemistry, pharmacology, behavioral pharmacology and psychological effects of nicotine and nicotine analogues. [801130, 1003060638-0643, Cipollone produced; Rothgeb produced]

By 1981, the Comparative Psychology Program had been renamed the Behavioral Pharmacology Program under the direction of Victor DeNoble. The objectives were stated as follows:

> I. To develop a better understanding of the behavioral pharmacological actions of nicotine, particularly the action which reinforces smoking behavior.
>
> II. Develop the empirical evidence which differentiates nicotine from the classical abuse substances.
>
> III. Use behavioral pharmacological methods for evaluating the nicotine-likeness of nicotine analogues. [1003293130-3137, Cipollone taken, defend.'s exhibit]

These objectives were pursued using the following main areas of study: Self-Administration, Discrimination Task, Prostration Syndrome, Withdrawal Syndrome, and Tolerance. The remainder of this section will discuss the various research projects conducted under these broad categories.

3. Termination of Behavioral Pharmacology Program

In July 1983, Patrick Sirridge of Shook, Hardy & Bacon wrote to Philip Morris' Assistant General Counsel Fredric Newman transmitting an analysis of DeNoble's published literature, unpublished manuscripts, and in-press manuscripts. [1005059920, Rothgeb privileged] The analysis concluded that "[r]esearch engaged in, as well as some possibly under consideration, by Philip Morris has undesirable and dangerous implications for litigation positions the industry takes in regard to smoking behavior. . . . In the final analysis, the performing and publishing of nicotine related research clearly seems ill-advised from a litigation point of view." [1005059921-9931 (p. 9931), Rothgeb privileged]

In spring 1984, DeNoble was terminated and the Nicotine Program was discontinued. Although there were no internal documents found stating the reasons why DeNoble and his program were terminated, it could be easily concluded that the unfavorable analysis of the program submitted by Philip Morris' legal counsel prompted DeNoble's termination and the program's cancellation.

4. Discontinued Studies

The following studies were conducted under the direction of Dr. Carolyn Levy who directed the Comparative Psychology Program and its successor the Behavioral Pharmacology Program until January 15, 1980. These studies were abandoned shortly after DeNoble joined Philip Morris. DeNoble was recruited by Philip Morris "to upgrade the behavioral pharmacology program." Discontinuation of these studies may well have been DeNoble's initial effort to improve this program.

a. Nicotine and Locomotor Activity

The activity monitoring studies were initiated to evaluate whether a measure of locomotion could serve as a screen for nicotine analogues. Previous studies had revealed that the following dosages of nicotine could suppress locomotor behavior: 0.05, 0.1, 0.2, and 0.4 mg/kg body weight. Basically this study had two objectives: first, to determine at what dose level nicotine produced the same effect as saline and second, to evaluate the effect of nicotine analogues.

The study revealed that nicotine produced a statistically significant decrease in locomotor activity on the first and second day relative to the saline group. On the third day a significant increase in activity was observed in the nicotine group, while on the fourth day the level of activity between the nicotine group

and the saline group did not differ. Studies were then designed to determine whether the variation in activity for the nicotine group could be attributed to the development of tolerance. DeNoble found that the nicotine injected rats increased locomotor activity with increased exposure to nicotine. He concluded that "the effects seen in the first study were due to the development of nicotine tolerance. . . ." Nevertheless, DeNoble decided to discontinue the locomotor technique for two reasons: first, problems interpreting the changes in activity had arisen and second, it was felt that the results obtained from this technique would "not add significantly to our testing program." [800620, 1003060599-0619 (p. 0608), Rothgeb produced; 1000384296-4318 (dup), Cipollone produced]

b. Tail Flick Test

The tail flick test had previously shown that nicotine produced analgesia (the inability to feel pain although conscious) in rats. Preliminary results were reported by Carolyn Levy regarding the tail flick test which was being evaluated for its usefulness in screening nicotine analogues and its stereospecificity on tail flick latency. In initial studies, both S-(-)- and R-(+)-nicotine elevated rats' tail flick latencies and reduced responsiveness to the painful thermal stimulus. The results of this test supported previous findings that nicotine had an analgesic effect on rats. However, some of the doses produced muscle spasms. This led to the development of another test that could be used to determine the analgesic effects of nicotine. This second test utilized hot water as the stimulus to the rat's tail.

In general, the effects on tail withdrawal were clearly observable and easily quantified. However, accurate measurements were not always possible due to tail quivers and jerks. "More disappointing, however, was the lack of an observed analgesic effect induced by nicotine."

Due to the above mentioned difficulties the tail flick method was abandoned. [800620, 1003060599-0619 (p. 0608-0610), Rothgeb produced; 1000384296-4318 (dup), Cipollone produced]

c. Place Preference Paradigm

The premise behind this technique was: if given a choice, animals preferred to remain in places where they had previously had positive experiences. Testing conducted with morphine clearly illustrated that rats preferred to remain in the chamber where they had been injected with morphine. Due to its effectiveness in illustrating the reinforcing properties of morphine, this technique was evaluated for its usefulness in studying the reinforcing effects of nicotine.

Rats that were given nicotine injections later failed to show a preference for either chamber. These results clearly demonstrated that nicotine's "reinforcing properties" were quite different from those associated with morphine. Thus, the place preference paradigm was not useful for assessing the potential reinforcing properties of nicotine and was discontinued. [800529, 1000046347-6355, Cipollone produced; Rothgeb produced; 800620, 1003060599-0619 (p. 3610-3614), Rothgeb produced; 1000384296-4318 (dup), Cipollone produced]

d. Cold Swim Test

In a stress mitigator study involving a cold swim test and its effects on rats' ability to cross a barrier in response to an electric shock, rats in groups pre-treated with nicotine and stressed in a cold swim had longer latencies to cross the barrier. Levy speculated that nicotine affected pain threshold and more experiments were planned to examine this possibility. [1003293314-3321, Cipollone taken, all redactions removed] This test was evidently abandoned, as no other reports were found.

5. Self-Administration

Philip Morris first began reviewing literature on nicotine self-administration in 1977 as part of the Comparative Psychology Program. Findings from non-Philip Morris research showed that rats could be trained to lever press for nicotine; however, none had clearly demonstrated that nicotine was acting as a reinforcer. [761201, 1003293166-3177, Cipollone exhibit] The 1980 Annual Report of the Behavioral Research Lab identified its first goal was to illustrate that nicotine functioned as an intravenously delivered reinforcer. Intravenous and intracerebral self-administration techniques were utilized to evaluate the reinforcing properties of nicotine and nicotine analogues. [800620, 1003060599-0619 (p. 0618), Rothgeb produced; 100384296-4318 (dup), Cipollone produced]

a. Nicotine Self-Administration

In October 1980 DeNoble and Carron reported that nicotine self-administration tests had been initiated. The rats established nicotine self-administration at a dose of 32 ug/kg/injection. In order to determine whether lever pressing was maintained by the contingency established between lever pressing and nicotine delivery, saline was substituted for nicotine. The substitution of saline failed to maintain responding. When nicotine was reintroduced, lever pressing rose again to the previous levels. The data showed that animals maintained nicotine self-administration due to the nicotine following the response (response-nicotine

contingency), rather than by other behavioral effects of the drug. From this study it was determined that nicotine could act as an intravenously delivered positive reinforcer. [801014, 1003060646-0655, Cipollone produced; Rothgeb produced]

Following confirmation that nicotine could function as a positive reinforcer, DeNoble identified the following studies as "essential":

(1) Study the dose-response curve under various schedules.

(2) Determine the effects of cholinergic antagonists and *agonists upon self-administration.

(3) Determine the substitutability of selected analogues.

(4) Demonstrate the following:

(a) that nicotine self-administration does not interfere with on-going behavior and

(b) that termination of nicotine access for self-administration does not produce behavioral impairment, or alter self-administration of other reinforcers (i.e., food, water, saccharin, etc.). [801126, 1000085385-5392, Cipollone produced; Rothgeb produced; 810327, 1003060566, 1003060567-0598 (p. 0571-0581), Cipollone produced; Rothgeb produced]

In the 1983 Annual Report for the Behavioral Pharmacology Lab, DeNoble and Mele listed four indicators of the reinforcing effects of nicotine: "1) a greater number of lever presses when nicotine was response-contingent than when saline was response-contingent; 2) a greater number of responses on the nicotine lever than on the activity lever; 3) a systematic decrease in the number of contingent infusions when nicotine was delivered noncontingently; and 4) systematic changes in lever pressing as a function of the nicotine dose." [830601, 1003060364-0441 (p. 0371-0378), Rothgeb produced]

(1) Effects of Fixed Ratio on Nicotine Self-Administration

DeNoble undertook studies to determine the effects of a fixed ratio (FR) size on both the response rate and nicotine intake. A fixed ratio refers to the number of responses required before the reinforcer is administered. [810327, 1003060566, 1003060567-0598, Cipollone produced; Rothgeb produced] Preliminary results revealed that the response rate first increased then decreased as a function of fixed ratio size. Further testing showed that lever pressing remained fairly consistent at a ratio of 6 and 7; an increase to FR 8 produced a decrease in lever pressing. The most crucial finding of this study was that the number of nicotine infusions and the resulting nicotine blood level remained relatively stable over several ratio schedules. This suggested that responding for intravenously delivered nicotine was maintained "at least in part by the nicotine blood level." [810824, 1002973585, 1002973586-3615 (p. 3597), Cipollone taken; Rothgeb produced; Shires taken] DeNoble concluded that when compared to responding rates for other intravenously delivered reinforcers, which were not specified, the nicotine rates were low, thus indicating that nicotine may be a weak reinforcing agent. [830601, 1003060364-0441 (p. 0378), Rothgeb produced]

(2) Effect of Mecamylamine or Hexamethonium on Nicotine Self-Administration

Rats were given pre-session treatments of two nicotinic cholinergic antagonists: mecamylamine, a centrally active compound, and hexamethonium, a nicotine antagonist which does not readily penetrate the CNS. Preliminary results showed that treatment with mecamylamine completely blocked the nicotine maintained responding. Treatments of hexamethonium had no impact on nicotine self-administration. (810327, 1003060566, 1003060567-0598 (p. 0581), Cipollone produced; Rothgeb produced] In January 1982, DeNoble stated that the results of pre-treating the rats with nicotinic-cholinergic antagonists had determined that the reinforcing effects of nicotine were centrally mediated. [820121, 1000084650-4657, Rothgeb produced]

This test was extended and the results completed in April 1982. DeNoble and Mele submitted a progress report which discussed the use of the following four compounds to block three neurochemical systems: hexamethonium, mecamylamine, naloxone (antagonist to narcotics), and haloperidol. The results using hexamethonium and mecamylamine were stated above. Pre-treatment with naloxone had no effect on nicotine self-administration. [820421, 1003060442,

1003060443-0503 (p. 0453-0459), Rothgeb produced] The results obtained at Philip Morris confirmed that naloxone was not effective as an antagonist of the positive reinforcing effects of intravenously delivered nicotine. [830601, 1003060364-0441 (p. 0379-0387), Rothgeb produced]

Haloperidol, a dopaminergic antagonist, decreased nicotine infusions by 35% for one day. Dopamine had previously been implicated in the central nervous system's response to reward. These results suggested that the reinforcing properties of nicotine may be partially governed by the dopaminergic system. [820421, 1003060442, 1003060443-0503 (p. 0453-0459), Rothgeb produced]

b. Acetaldehyde Self-Administration

DeNoble and Carron issued a progress report to Dunn in which they stated that other smoke components--including acetaldehyde--were being investigated for their potential reinforcing properties. [1003175754-5785; Rothgeb taken, deposition exhibit] The objectives of the acetaldehyde self-administration tests included the following:

(1) Establish intravenously delivered acetaldehyde as a positive reinforcer;

(2) Obtain a dose response function under unlimited acetaldehyde access conditions;

(3) Examine the effects of fixed-ratio size on response rates and acetaldehyde intake; and

(4) Determine the changes in the uptake, storage, and release of cholinergic, catecholaminergic, serotonergic, and other neurotransmitter systems on self-administration of acetaldehyde. [p. 5754-5755]

Studies were initiated to determine whether acetaldehyde could function as a reinforcer by itself or whether it acted as an agonist or antagonist to the positively reinforcing effects of nicotine. Once lever pressing stabilized, saline was substituted for the acetaldehyde. After lever pressing for saline was stabilized, acetaldehyde was reintroduced. Acetaldehyde elicited 10.1 responses per hour while saline elicited only 4.75. Upon the reintroduction of acetaldehyde, the response rate returned to presaline levels. These results clearly demonstrated that acetaldehyde alone acted as a positive reinforcer. [810327, 1003060566, 1003060567-0598 (p. 0581-0586), Cipollone produced;

Rothgeb produced; 810824, 1002973585, 1002973586-3615 (p. 3598-3602, Cipollone taken; Rothgeb produced; Shires taken]

(1) Effects of Dose on the Number of Responses and Acetaldehyde Intake

Acetaldehyde self-administration was stabilized in rats. Doses were then presented in ascending and descending order. The rats were kept at one dose for at least 7 days. No data were provided regarding ascending doses. However, the results showed that after a decrease in the dose the rats responded initially by increasing the number of responses and then decreasing. The relationships between dose, responding, and intake were similar to those obtained from other events which maintained behavior (i.e., food, water, saccharin, etc.). [820421, 1003060442, 1003060443-0503 (p. 0452-0453), Rothgeb produced]

(2) Effects of Fixed Ratio on Acetaldehyde Self-Administration

Ratio data were developed in order to evaluate the relative reinforcer effectiveness of a compound. This technique was run using only one rat. Results showed that the number of lever presses increased as a function of the ratio size up to FR 15. It was determined that the intake, measured as mg/kg/day, decreased over the first three ratios, then remained constant over the next five. When compared to acetaldehyde,

> (-)-nicotine did not maintain lever pressing at these high ratios. This indicates that acetaldehyde, at similar doses to (-)-nicotine, is more effective at maintaining behavior. [820421, 1003060442, 1003060443-0503 (p. 0453), Rothgeb produced]

(3) Effects Of Haloperidol Or Naloxone Injections On Acetaldehyde Self-Administration

It was suggested that the reinforcing mechanism of acetaldehyde might be due to the formation of tetrahydroisoquinolines (TIQs), which are derived from catecholamines. TIQs were known to interact with a variety of membrane systems. More specifically, it was hypothesized that the effect of acetaldehyde on the CNS was mediated by the formation of TIQs. DeNoble decided to study TIQs and determine whether they could function as intravenously delivered positive reinforcers.

The specific TIQs studied was carboxysalsolinol. DeNoble found that rats readily self-administered this compound at a high response rate, which was delivered at a dose of 160 ug/kg/infusion. Hyperactivity was observed in the animals with the main symptom being motor activation. When saline was substituted a gradual decrease in lever pressing was noted. Reintroduction of the TIQ caused responding to rise to the previous levels. DeNoble concluded that carboxysalsolinol was a very powerful reinforcer. [810824, 1002973585, 1002973586-3615 (p. 3604-3605), Cipollone taken; Rothgeb produced; Shires taken]

Additional efforts to develop an understanding of the reinforcing properties of acetaldehyde in the CNS involved blocking the endogenous opiate receptors and preventing the release of dopamine. Following this, the rats were infused with acetaldehyde. Once acetaldehyde was established as a reinforcer the rats were injected with either naloxone or haloperidol.

Treatment with naloxone, at doses of 1.5 and 3.0 mg/kg/ip, produced no major changes in the number of self-administered infusions. These findings suggested that the endogenous opioid system was not involved in maintaining acetaldehyde self-administration. Treatments of 0.5 mg/kg/ip haloperidol reduced the number of self-infusions to below the saline level. DeNoble found these results to be particularly interesting in light of the speculated role of TIQs acting as the reinforcing agent in cigarettes; however, he did not expand on this. [820421, 1003060442, 1003060443-0503 (p. 0453-0459), Rothgeb produced]

(4) Suggested Conversion of Acetaldehyde to Ethanol

In April 1982 Ray Dawson, consultant for Philip Morris, sent a letter transmitting his thoughts on the possible reinforcing mechanism of acetaldehyde. Dawson stated that although the behavioral aspects of nicotine and acetaldehyde self-administration were important, the biochemical factors needed to be investigated. One possible biochemical complication was the conversion of acetaldehyde to ethanol, followed by the accumulation of ethanol in blood, brain or some other organ.

Dawson suggested that due to the equilibrium constant of alcohol dehydrogenase (an enzyme that breaks down alcohols), acetaldehyde of whatever origin will be converted largely to ethanol (approximately 10 molecules ethanol for every 1 molecule acetaldehyde). Dawson also proposed that nicotine played a role in this conversion. He suggested that:

> the net effect of nicotine administration may be to elevate ethanol content of some organ, and of the co-administration of nicotine and acetaldehyde to elevate ethanol content still a little more in some additive fashion. [820415, 1003186525-6526, Rothgeb taken; Shires taken]

Dawson later wrote to Osdene regarding the possibility that acetaldehyde reinforced nicotine through its conversion to ethanol. [831228, 1000081609-1610, Rothgeb produced] Dawson suggested that "the effects of acetaldehyde as a reinforcing agent to nicotine may result from an in vitro conversion to ethanol." [831228, 1000081611-1613, Rothgeb produced] Apparently this suggestion was not actively pursued.

c. Nicotine-Acetaldehyde Self-Administration

DeNoble and Carron decided to study the combined effect of nicotine and acetaldehyde on self-administration. One reason for studying the self-administration of a combined nicotine-acetaldehyde was due to the fact that both compounds had positive reinforcing effects when delivered intravenously to rats. [820421, 1003060442, 1003060443-0503 (p. 0463-0466), Rothgeb produced]

The objectives were to:

(1) Examine the nicotine-acetaldehyde interactions on self-administration behaviors; and

(2) Examine the neurochemical correlates of the reinforcing properties of nicotine and acetaldehyde. [810327, 1003060566, 1003060567-0598 (p. 0568), Cipollone produced; Rothgeb produced]

In August 1984 DeNoble reported on the combined effects. The dose consisted of 4.0 ug/kg/infusion acetaldehyde and 4.0 ug/kg/infusion nicotine. The animals maintained responding at this combined dose. When the animals were given the same dose of each compound separately, responding behavior was not maintained. The combined influence of nicotine and acetaldehyde was greater than the two doses added together, suggesting a synergistic effect. [810824, 1002973585, 1002973586-3615 (p. 3603), Cipollone taken; Rothgeb produced; Shires taken]

The interaction between nicotine and acetaldehyde was determined to be a modification of the pharmacological effect of one

compound by the other. DeNoble and Mele later reported that when either nicotine or acetaldehyde was removed from the mixture, the number of level presses decreased. This further supported the finding that when both compounds were functioning as reinforcers, they interacted. [820421, 1003060442, 1003060443-0503 (p. 0466), Rothgeb produced]

In the 1983 Annual Report of the Behavioral Pharmacology Program, DeNoble and Mele stated that they hoped to determine the optimal ratio(s) of nicotine and acetaldehyde combinations that would result in an enhanced positive reinforcing effect. Preliminary results revealed that acetaldehyde alone maintained responding at a higher rate than nicotine at equivalent mg/kg doses. Also, several combinations of acetaldehyde and nicotine maintained behavior above the levels of either compound when presented alone. They determined that the optimal reinforcing effect was obtained by 2-8 ug/kg nicotine added to 16.0 ug/kg acetaldehyde. [830601, 1003060364-0441 (p. 0388-0392), Rothgeb produced]

The fact that Philip Morris recognized commercial application of these findings was reflected in notes made at a meeting in which DeNoble presented information from research conducted on nicotine and acetaldehyde. It is believed that these notes were written by Judy John; they were found in her files and appeared to be her handwriting. John noted that both nicotine and acetaldehyde had been shown to be positive reinforcers and that these two compounds interacted. One goal of the research was to determine the maximal reinforcing ratio of acetaldehyde to nicotine. John also noted that data for nicotine and acetaldehyde predicted sales at 96% accuracy; however, the data to which John was referring to is not known. It is interesting to note that "additive effects accounts for 96% sales." This seemed to imply that smokers were buying and smoking cigarettes due to the acetaldehyde-nicotine content. John further noted that the higher each number for acetaldehyde and nicotine, the higher the predictability. Plaintiff could interpret these statements as indicating that Philip Morris was interested in achieving the optimal reinforcing ratio of acetaldehyde to nicotine in order to increase sales. [830628/E, 1003582081-2082, Rothgeb taken; Shires taken]

d. Frustrative Non-Reward

In the 1982 Behavioral Pharmacology Progress Report DeNoble and Mele discussed the frustrated non-reward (fnr) technique. The test involved establishing a fixed ratio in the presence of a white light, which was on until the ratio was completed and the reinforcer delivered. Upon completion of the ratio (fulfilling the number of responses required for the reinforcer to be delivered) and delivery of the reinforcer, the

white light went out and two red lights came on. At regular intervals two correctly emitted responses were not reinforced. The lights switched, yet the reinforcer, in this case a food pellet, was withheld. This produced behavior which was counterproductive to obtaining the next reinforcer.

> The results show that (-)-nicotine, at the doses tested, had no effect on the induced behavioral change. However, acetaldehyde reduced the disruptive effects of food emission. In addition, the effect was dose related. [820421, 1003060442, 1003060443-0503, p. 0488-0489), Rothgeb produced]

Further discussion of these studies suggested that nicotine enhanced the fnr behavior. Compound 44, another smoke component tested, reduced the fnr behavior in a dose related fashion. This compound was probably acetaldehyde. [820512, 1002972797-2803, Rothgeb produced] Pages later noted that acetaldehyde apparently had some moderating effects on fnr behavior. [830816, 1002973179-3180, Rothgeb produced]

6. Discrimination Testing

a. Nicotine - Nicotine Analogue Discrimination

The discrimination task was utilized to determine the rats' ability to distinguish between two internally arising stimuli (interoceptive stimuli) produced by the compounds tested.

Philip Morris began work in this area as outlined in the 1978 Plans and Objectives. Carolyn Levy planned to study Discriminant Response Learning in animals where animals were trained to discriminate nicotine injections from saline injections. She wrote that since "nicotine's reinforcing action for smokers depends upon its action on the CNS, the nicotine discrimination paradigm is useful as a tool in screening compounds for their ability to produce nicotine-like CNS effects." [1003293314-3321, Cipollone taken, all redactions removed] Philip Morris was planning to use the same approach to study the nicotine cuing properties of d-nicotine and other alkaloids such as m-nicotine, anabasine, dihydro-m-nicotine, nornicotine, n-methyl-anabasine and myosmine, and acetylcholine. Philip Morris' goal was to determine whether the drug discrimination procedure would be valuable to screen nicotine analogues. Philip Morris anticipated learning about the central effects of nicotine and answering the question, "Is this compound like nicotine?"

In a March 13, 1980, report, DeNoble identified four nicotine analogues which were to be tested for the production of nicotine-like interoceptive response. [1001521180-1182, Rothgeb produced; 800512, 1003293058-3060, Cipollone taken; Rothgeb produced; Shires taken The discrimination task had proven to be a very effective means for screening analogues and would continue to be used. DeNoble hoped to utilize the test more efficiently and therefore derive more information from it. [800424, 1003060644-0645, Cipollone produced; Rothgeb produced]

In July 1980 DeNoble reported that two nicotine analogues, dl-3-dimethylaminomethyl pyridine and 2'-methylnicotine, produced nicotine-like interoceptive responses. [800710, 1003293054-3056, Cipollone taken; Rothgeb produced; Shires taken; 80018, 1000128797-8804, Cipollone taken; Rothgeb produced; Shires taken]

2'-Methylnicotine produced responding in 100% of the animals at a dose of 0.4/mg/kg body weight; doses higher than this produced incomplete responding, identified as failure to complete the ratio in the time allotted. Studies were planned to determine the dose response curve using 2'-methylnicotine, in order to compare its potency to that od d,1-nicotine and 1-nicotine. Additional tests were planned to determine the effectiveness of 2'-methylnicotine when the animals were given preinjections of mecamylamine or hexamethonium. The results obtained from this study would determine whether discrimination of 2'-methylnicotine was mediated centrally or peripherally. [800818, 1000128797-8804, Cipollone taken; Rothgeb produced; Shires taken]

Another nicotine analog, metanicotine, produced lever pressing in the animals. At a dose of 4.0 mg/kg, 50% of the animals responded with nicotine cues; when the dose was increased to 8.0 mg/kg, 100% of the animals responded. [801014, 1003060646-0655, Cipollone produced; Rothgeb produced]

By February 1981 two more analogues had been evaluated using the discrimination task. These analogues, d,1-N-methyl-2-(3-picolyl) pyrrolidine and d,1-N-methyl-beta-(pyridyl ethyl) pyrrolidine, produced nicotine-like cues; the doses required were 8-10 times the training dose of (-)-nicotine. [810211, 1003289229-9232, Cipollone taken; Shires taken; 1001400402-0405 (dup), Rothgeb produced]

Other analogues were tested in the discrimination task. It was found that cis 2'-methylisonicotine was inactive at all doses. At a dose of 3.2 mg/kg, trans 2'-methylisonicotine caused 33% of the rats to respond on the nicotine lever, 33% on the saline

lever, and 33% failed to respond. Doses of 0.4 mg/kg - 1.6 mg/kg produced lever pressing on the saline lever in 100% of the rats. [810310, 1003289226-9228, Cipollone taken; Rothgeb produced; Shires taken]

In late 1981, it was decided that the discrimination task and intraventricular administration techniques would be used to develop a structure/activity relationship for the nicotine analogues. [811105, 1000084973-4981, Rothgeb produced]

The discrimination task alone was useful as a routine screen for behaviorally active nicotine analogues, but by April 1982 it was decided to employ several additional tests to better characterize their activity. It was planned to use these more sensitive measures to determine the relative potencies between the nicotine analogue and the duration of the effect in the central nervous system. [820421, 1003060442, 1003060443-0503, Rothgeb produced] However, no further reports were found.

b. Acetaldehyde Discrimination

In March 1981 DeNoble and Carron submitted a progress report to Dunn discussing the rationale underlying their efforts to establish an acetaldehyde discrimination study. First, acetaldehyde had been shown to act as an intravenously delivered reinforcer; second, the data indicated that carboxysalsolinol (TIQ) was also a reinforcer. In this study they hoped to determine whether the effects of acetaldehyde were similar to TIQs. [1003175753, 1003175754-5785 (p. 5768-5773), Rothgeb taken; Shires taken; 1003060566, 1003060567-0598 (dups) Cipollone produced; Rothgeb produced; 1000040398-0401 (partial dup) Rothgeb responsive but privileged (sent to Mr. Newman)]

The Behavioral Pharmacology Plans and Objectives for 1984 stated that the discrimination task, in conjunction with multiple schedule techniques, would be utilized to elucidate further the behavioral profile of acetaldehyde. [830906, 1003060131-0132, Rothgeb produced] No further data or results were found.

c. Nicotine-Acetaldehyde Discrimination

The self-administration tests had clearly shown that there was a behavioral interaction between nicotine and acetaldehyde. The discrimination study was undertaken to determine whether the interaction between nicotine and acetaldehyde was specific to self-administration or whether it could be extended to other behavioral tests. The animals were pre-treated with varying doses of acetaldehyde, and then the percent of nicotine-correct responding

was determined as a function of each acetaldehyde pretreatment dose. "It appears that the pretreatment with the various doses of acetaldehyde did not improve the nicotine discrimination. In addition, it also appears that the pretreatment did not reduce the effectiveness of this nicotine dose (0.05 mg/kg/sc)." [830601, 1003178534-8615 (p. 8564), Rothgeb taken; Shires taken; 1003060364-0441 (dup), Rothgeb produced; 1005215287-5296 (partial dup), Rothgeb taken; Shires taken] In a handwritten summary of the 1983 accomplishments, it was concluded that:

> Blocking studies and discrimination tests suggest that acetaldehyde and nicotine are acting on separate neural systems. [1003177545-7546, Rothgeb taken; Shires taken]

7. Prostration Syndrome

DeNoble wanted to use the prostration syndrome, which was developed by Dr. Leo Abood, to determine the relative potency of nicotine analogues. DeNoble used rats that had been trained to lever press. [800424, 1003060644-0645, Cipollone produced; Rothgeb produced] Dr. R. A. Pages described the prostration syndrome as follows: after a 5 ug intraventricular infusion of nicotine, the rats went into a temporary "paralysis"; they had no control over their extremities, yet seemed to be aware of their environment. After about 5 minutes, the rats began to recover, they gained control over their limbs and were able to move around. After another 5 minutes, the rats recovered sufficiently to lever press.

A March 13, 1980, report stated that intraventricular injections of l-nicotine produced the prostration syndrome and that it appeared to be specific to nicotine-cholinergic activity. DeNoble used a behavior rating scale that had successfully been used to screen nicotine analogues for gross behavioral and CNS effects. [1001521180-1182, Rothgeb produced; information duplicated in May 12, 1980, report: 1003293058-3060, Cipollone taken; Rothgeb produced; Shires taken]

DeNoble later reported that both (-)-nicotine and (+)-nicotine induced the prostration syndrome, with (+)-nicotine being only 1/10 to 1/20 as active. The prostration syndrome was to be used to examine the relative potencies of nicotine analogues, particularly those that demonstrated nicotine-like effects in the discrimination tests. [800424, 1003060644-0645 Cipollone produced; Rothgeb produced] Studies were to be conducted to determine the sites of action, the extent of the behavioral prostration, and the effect of intraventricular injections of nicotine. [800620, 1003060599-0619 (p. 3618-3619), Rothgeb produced]

a. Effects of Intraventricular Injections of Nicotine and Nicotine Analogues on Activity and Schedule-Controlled Behavior

Tests were run to compare the effect of 2'-methylnicotine with those of (-)-nicotine. It was found that 2'-methylnicotine was equally as active as (-)-nicotine. [800710, 1003293054-3056, Cipollone taken; Rothgeb produced; Shires taken] Although the prostration syndrome was very useful, it could not detect possible prolonged changes in the CNS. In contrast, schedule-controlled behavior was sensitive to CNS changes; it allowed for the development of a highly stable and reproducible baseline of behavior dependent on the integrity of the CNS. Rats that were nicotine infused displayed behavioral disruptions of 10-12 minutes post infusion. EEG readings taken by Dr. Leo Abood revealed that following intraventricular injections of nicotine rats displayed a recovery of baseline hippocampal activity at 10-12 minutes post infusion. These two pieces of data demonstrated that prolonged CNS changes had indeed occurred. [800818, 1000128797-8804, Cipollone taken; Rothgeb produced; Shires taken]

In an attempt to identify the neuroanatomical structures which mediated the prostration syndrome, Dr. Abood's assistance was enlisted. When Abood blocked several specific brain regions, he found that only the inhibition of the lateral vestibular nucleus caused the prostration syndrome to be blocked. [1002973585, 1002973586-3615 (p. 3605), Cipollone taken; Rothgeb produced; Shires taken] These results suggested that the prostration syndrome was mediated in the lateral vestibular nucleus.

b. Supersensitivity

Supersensitivity was defined as the "chronic inactivation of postsynaptic receptors in the CNS [which] produces an increased sensitivity (supersensitivity) of these receptors to the appropriate agonist." Due to the lack of data concerning this phenomenon, the Behavioral Pharmacology group decided to conduct studies to induce nicotinic receptor sensitivity in the CNS.

The prostration syndrome induced by nicotine was used as a behavioral index of supersensitivity. A preliminary test was conducted using one rat. The rat was given chronic doses of mecamylamine for 14 days. On day 15 the prostration produced by a low dose [2.5 ug] of nicotine was enhanced relative to that observed before chronic mecamylamine treatment. [820421, 1003060442, 1003060443-0503 (p. 0501-0502), Rothgeb produced]

This test was later replicated using several rats. They were initially given a nicotine infusion, and the latency to complete the first ratio was measured. Then the rats were given chronic doses of mecamylamine. Upon termination of the mecamylamine dose, they received an infusion of nicotine and the latency was measured. This procedure of chronic mecamylamine treatment followed by a nicotine infusion was repeated once more.

> Chronic mecamylamine treatment failed to produce an enhanced behavioral response to nicotine. This suggests that under the conditions of the present study, chronic blockade of central nicotinic receptors did not result in an up-regulation [an increase in the number of post-synaptic receptors] that was detected at the behavioral level. [8588]

These studies were extended to include the "systematic manipulation of the dose, duration and type of receptor blocker administered, the dose and route of administration of nicotine, and the behavioral dependent variable," to delineate the functional significance of central nicotinic receptors in a variety of behaviors. [830601, 1003178534-8615 (p. 8584-8589), Rothgeb taken; Shires taken; 1005215287-5296 (partial dup), Rothgeb taken; Shires taken; 1003060364-0441 (dup), Rothgeb produced] In September 1983 this project was still active; however, no data were reported. [830906, 1003060131-0132, Rothgeb produced]

8. Withdrawal Syndrome

a. Termination of Nicotine

In November 1980 Dunn's plans and objectives for the Behavioral Pharmacology Lab included a proposed study to demonstrate "that termination of nicotine availability for self-administration does not produce behavioral impairment, or alter self-administration of other reinforcers. . . ." This objective clearly indicated an intent to show that nicotine was not an "addictive" drug and did not result in the development of physical dependence. [1000085385-5392, Cipollone produced; Rothgeb produced]

Dunn submitted the accomplishments to the Behavioral Pharmacology Program to Osdene in December 1980. In this report DeNoble expressed his views about termination of chronic nicotine administration.

> It is our belief that the magnitude of change observed on nicotine cessation reflects behavioral adjustments to the removal of a positive reinforcer, not a withdrawal syndrome.

A study was designed which would determine what effect termination of chronic nicotine administration had on a rat's performance of a complex multiple fixed ratio fixed interval schedule. Changes in performance would be interpreted as reflecting changes in CNS integrity. [801223, 1003293284-3293, Cipollone taken; Rothgeb taken; Shires taken] However, DeNoble pointed out that the results obtained from this study would yield information regarding the possible withdrawal effects of nicotine, not cigarette smoking. [1003175753, 1003175754-5785, Rothgeb taken; Shires taken; 1003060566, 1003060567-0598 (dups), Cipollone produced; Rothgeb produced; 1000040398-0401 (partial dup), Rothgeb responsive but privileged (sent to Mr. Newman)] From the results obtained, it was concluded that "there is not a physical dependence produced by chronic nicotine administration." [810603, 1000040405-0410, Cipollone taken; Rothgeb produced; Shires taken]

In a later experiment, rats were given chronic nicotine doses and then challenged with mecamylamine. "The mecamylamine challenge had no effect on the schedule-controlled behavior, indicating an absence of physical dependence on nicotine." There were plans to repeat these tests because of the significance of the findings. [810824, 1002973585, 1002973586-3615 (p. 3611-3613), Cipollone taken; Rothgeb produced; Shires taken]

> [T]he absence of a withdrawal syndrome in this and other animal studies . . . combined with the lack of consistency in the data on humans suggests a more general interpretation, such as a learning mechanism whereby the interpretation of a well learned response that leads to positive reinforcement results in a variety of behavioral physiological changes which are reported by humans and are interpreted as withdrawal syndrome. [820421, 1003060442, 1003060443-0503, Rothgeb produced]

Shortly after this report, Charles submitted the Plans and Objectives for 1983 to Osdene which contained the following objective.

> Behavioral Pharmacology . . . studies on nicotine and acetaldehyde regarding reinforcing effects, physical and behavioral dependence and the development of tolerance will contribute vital information for the design of a product with the most desirable smoke properties. [820728, 1003479455-9461, Rothgeb taken; Shires taken]

This could be interpreted by plaintiff as evidence that Philip Morris was concerned primarily with trying to develop a marketable product with maximal reinforcing properties.

b. Termination of Acetaldehyde

In the June 1983 Annual Report of the Behavioral Pharmacology Lab, DeNoble and Mele discussed the results obtained from studies on the termination of chronic acetaldehyde administration. Two procedures had been used to determine whether termination produced a withdrawal syndrome. The first study involved iv infusion of acetaldehyde (3.0 mg/kg) every 20 minutes for 10 days. Saline was substituted for two days. The acetaldehyde was then reintroduced at 6.0 mg/kg every 40 minutes for 20 days. The animals were observed during the saline periods for any signs of withdrawal, such as apprehension, tremor, piloerection, impaired motor activities, convulsions, or loss of appetite.

The data revealed that neither food intake nor activity was altered when saline was substituted. DeNoble concluded that "termination of chronic acetaldehyde administration does not result in a withdrawal syndrome. In addition, observations by three individuals failed to detect any overt signs of a withdrawal syndrome."

In the second, more sensitive procedure, rats were trained to lever press under an FR 32 schedule for a food pellet. Once established, the rats were infused with acetaldehyde every 20 minutes over a 24-hour period. Food was available under an FR 32 schedule for 15 minutes every 2 hours, 45 minutes. This procedure allowed observation of multiple samples of behavior within the 24-hour period previously shown to be sensitive to drug withdrawal.

> The failure to find any disruption in food reinforced lever pressing when chronic acetaldehyde was terminated across several doses and across several dosing schedules is strong evidence that chronic acetaldehyde intake does not result in physiological dependence. In addition, this data [the results discussed above], combined with previous data shows that acetaldehyde does not interact with an endogenous opioid system. [830601, 1003178534-8615 (p. 8565-8570), Rothgeb taken; Shires taken; 1005215287-5296 (partial dup), Rothgeb taken; Shires taken; 1003060364-0441 (dup), Rothgeb produced]

c. Termination of Nicotine-Acetaldehyde Combination

In October 1983 a study was performed to determine whether termination of chronically administered nicotine-acetaldehyde combinations resulted in a physiological dependence syndrome. No disruption in food reinforced lever pressing upon termination of chronic nicotine-acetaldehyde administration was observed. This provided strong evidence that chronic exposure to the combination of compounds did not result in physiological dependence. [831005, 1003060631-0633, Rothgeb produced]

9. Tolerance

Tolerance was defined as a diminished effect of a substance with its repeated administration. Two mechanisms that may have caused pharmacological tolerance were suggested. The first mechanism involved pharmacokinetic factors which altered the effective concentration of the active agent at the receptor. The second mechanism involved a decrease sensitivity of the receptor, even though the concentration of the active agent at the receptor remained unaltered. [1003060442, 1003060443-0503 (p. 0489-0500), Rothgeb produced]

a. Behavioral Tolerance and Metabolic Tolerance

In October 1980 DeNoble and Mele submitted a progress report to Osdene. An extension of the prostration syndrome testing had led to studies on tolerance. The findings which prompted these studies involved the following: rats that had been infused with 5 ug l-nicotine were then given twice the dose, 10 ug. The infusions were administered at least 7 days apart, and it was noted that the daily response rate varied less than 15% from day to day. DeNoble and Mele observed that the duration of the suppression in the response rate produced by the 10 ug dose was shorter than the length of suppression produced by the 5 ug dose.

The most likely explanation of these results was that behavioral tolerance had developed. "Behavioral tolerance is a diminished [behavioral] effect of a compound with repeated exposure to that compound without the induction of metabolic tolerance." In order to study this, the requirement for reinforcement was increased from 16 to 32. Once the rats were stabilized on the FR 32, they were infused during the daily session with 5 ug of nicotine on two occasions, 5 days apart. The second infusion of nicotine had a diminished effect, suggesting that some degree of tolerance had developed. DeNoble planned a series of studies which would more accurately characterize the development of tolerance. [801014, 1003060646-0655, Cipollone produced; Rothgeb produced]

DeNoble's Plans and Objectives for 1983 included two proposals which dealt with tolerance. The first study involved examining the interaction between behavioral and metabolic tolerance induced by chronic nicotine exposure. The research was designed to examine the relative contributions of metabolic and behavioral influences on the development of tolerance. The second study focused on developing a behavioral profile of nicotine-induced tolerance utilizing the cross tolerance method. By using this method, DeNoble would obtain information about the nature of tolerance mechanisms in the CNS. In addition, these data would be used as a basis for determining the specificity of nicotine analogues in producing nicotine-like activity in the CNS. [820000/E, 1003186551-6554, Rothgeb taken, Shires taken; 820720, 1003060135-0140, Rothgeb produced; 1003060155-0160 (dup), Rothgeb produced]

DeNoble reported the preliminary results of a study being conducted to determine the interaction of behavioral and metabolic tolerance following chronic nicotine administration. He found that after 16 days of chronic nicotine administration at a dose of 0.8 mg/kg/sc, rats showed signs of tolerance. This testing was to be continued until tolerance was complete. [820827, 1001400456, Rothgeb produced]

b. Influence of Behavioral Factors on the Development of Tolerance

In April 1982 DeNoble and Mele suggested that tolerance might be influenced by certain behavioral factors (i.e., learning or performance). One factor which influenced the development of tolerance was whether or not the compound disrupted on-going behavior such that the rate of frequency of reinforcement delivery was altered. It had been determined that tolerance was more likely to occur, or would occur more rapidly, if the compound produced a loss of reinforcement as opposed to the reinforcement frequency remaining unaffected. [820421, 1003060442, 1003060443-0503 (p. 0498), Rothgeb produced]

In the 1983 Behavioral Pharmacology Annual Report, Mele stated that the development of tolerance to many of the behavioral and physiological effects of nicotine after repeated administration was well documented.

> At the present time, however, it is unclear whether the development of tolerance to the behavioral effects of nicotine is due to altered concentrations of nicotine at the receptor

> (pharmacokinetic tolerance), to altered sensitivity of nicotine receptors (pharmacodynamic tolerance), to certain behavioral and environmental factors, or to some combination of the above.

The test used to determine whether behavioral factors were involved in the development of tolerance to nicotine was the before/after dosing paradigm. This technique involved chronic dosing two groups, one before and one after the experimental session. The performance of the group dosed before the session was altered, whereas the performance of the group dosed after the session was not altered. Following the development of tolerance in the before group, the after group was given the nicotine pre-session to test for tolerance.

> Nicotine decreased response rates averaged over the total 30 minutes . . . and response rates during the first six minutes of the session . . . in a dose dependent manner. Reductions in response rates were most pronounced during the first six minutes of the session, indicating that some recovery occurred during the latter portions of the session. The dose-effect functions for the before and after groups were similar.

The reductions in response rate for the before group on day 1 of chronic dosing were similar to those obtained initially. The magnitude of the response rate reductions decreased over sessions of chronic tolerance. No impact was made on the responding rate of the after group. They determined that after 30 days of chronic dosing, the before group was more tolerant to nicotine than was the after group.

In an effort to gain further data on tolerance, the decision was made to determine whether the after group had developed any tolerance to nicotine. In order to do this, the effects of (-)-nicotine on day 31 of the chronic dosing period were compared to those obtained during the initial dose-effect study. Results showed that the reductions in response rate on day 31 were slightly, yet significantly, smaller than the reductions observed initially. These results indicated that some tolerance had developed with chronic post-session dose-effect determination which suggested that some degree of tolerance persisted in each group.

The findings obtained from this series of tests suggested that the development of tolerance to nicotine had two elements.

The major factor involved was a behavioral adaptation of the organism to the disruptive effects of nicotine on the schedule-controlled responding (behavioral tolerance). A secondary factor, considered to be fairly minor, was the effect of nicotine on FR responding which arose following the chronic administration. This secondary component may have reflected pharmacokinetic and/or pharmacodynamic mechanisms, however, further studies would have to be conducted in order to reach a definite conclusion.

The main conclusion reached in these studies was that tolerance developed to a greater degree in the group receiving doses before the session than those which were dosed after.

> [T]he development of tolerance to nicotine appears to be highly dependent on factors arising from the nicotine-induced disruption of FR responding, rather than on factors resulting from the mere repeated administration of nicotine.

c. Cross Tolerance

Cross tolerance was defined as a state which exists between two substances when the establishment of tolerance to one substance results in tolerance to the second substance. [820421, 1003060442, 1003060443-0503 (p. 0500-0501), Rothgeb produced] Testing was conducted on the nicotine analogue 2'-methylnicotine. The rats were first given 5 ug of l-nicotine; five days later the rats received 5 ug of 2'-methylnicotine. The results showed that the 2'-methylnicotine produced less suppression of the response rate under FR 32. These findings suggested that there was cross tolerance of 2'-methylnicotine to l-nicotine and/or a diminished peripheral effect. [801014, 1003060646-0655, Cipollone produced; Rothgeb produced] Dunn later confirmed that the results from the schedule-controlled behavior had shown the 2'-methylnicotine to have cross tolerance with nicotine. [801111, 1003293045-3048, Cipollone taken; Rothgeb produced; Shires taken]

Testing was conducted using two isomers of nicotine: (-)-nicotine, the naturally occurring isomer and (+)-nicotine, the unnatural isomer. This study was designed to provide data on the relative contribution of central and peripheral nicotinic receptors underlying the behavioral effects of stereoisomers of nicotine. The results indicated that the optically pure isomers of nicotine differed primarily in potency. [830601, 1003060364-0441 (p. 0408-0410), Rothgeb produced]

IV. SPONSORED RESEARCH

A. University of Rochester (Abood)

1. Overview

Philip Morris corresponded with Abood and cultivated a relationship with him throughout 1978 before sponsoring his research in 1979. Abood had had several years of CTR grants for his CNS research, but Philip Morris had expressed concern about the nature of his CTR work and about some of the implications of his stated goal to find an antagonist to nicotine. Nevertheless, Abood terminated his CTR grant work and signed agreements with Philip Morris for its sponsorship. Philip Morris funded Abood with a grant, hired him as a consultant for his advice on the Nicotine Program, and contracted with him to study proprietary compounds developed by Philip Morris.

There was no documentation reflecting why or when Abood's grant, consultancy and contract were terminated. On March 7, 1984, Philip Morris sent $40,250 to the University of Rochester to cover the first six months of the sixth year of Philip Morris' grant to Abood. [1000127311-7312, not produced] On March 8, 1984, Abood submitted a progress report for the period January 1983 to April 1984, with a request for continuing support into 1985. [1002973383-3392, not produced] Evidently, at least six months of Abood's proposal for the period 1984-1985 was funded. No other documents were found. Abood's work with Philip Morris may have ended in mid 1984 after Philip Morris cancelled its Nicotine Program.

2. Association with Philip Morris

Osdene attended a meeting at CTR on November 22, 1977, where there was a discussion regarding CNS research sponsored by CTR. At this meeting, Leo Abood made a presentation regarding his CTR research grant to localize and isolate nicotine receptors and to characterize their biochemical make-up. [1000036595-6596, not produced] Philip Morris had grave concerns concerning the stated aims of Abood's research to make a clinically acceptable antagonist to nicotine. In a January 10, 1978, memorandum, Osdene wrote that, "This goal would have the potential of putting the tobacco manufacturers out of business." [1000036519-6520, Cipollone privileged]

Considering Osdene's view of Abood's work, it was not entirely clear why Osdene opened a dialogue with Abood. Nevertheless, over the course of 1978, Philip Morris and Abood

corresponded and arranged visits. On January 25, 1978, Osdene arranged to visit Abood accompanied by other Philip Morris scientists. [1000127938, not produced] Abood made arrangements to visit Philip Morris in June 1978. [1000127937, not produced] One clue that Philip Morris was considering Abood's, as well as other scientists', possible contribution to the Philip Morris Nicotine Program was evident by Seeman's March 15, 1978, memorandum to Osdene in which he expressed his opinion that an effective Nicotine Program required both peripheral and CNS bioassays. He stated that CNS studies represented the most complex state of the art concepts. Seeman mentioned Abood's development of the prostration syndrome bioassay and other work related to the isolation and characterization of nicotine CNS receptors. Seeman's point was that outside researchers including Abood could help Philip Morris' research plan, but that Philip Morris "must devise not a shopping list for todays needs but a policy for the program as a whole." [1000128660-8661, Cipollone taken, defend.'s exhibit] It was possible that despite Philip Morris' discomfort with Abood's CTR work, Philip Morris still recognized Abood's leadership in this area of research and wished to learn and to improve its own Nicotine Program.

A June 22, 1978, memorandum from Ahrensfeld to Holtzman reported that Abood had approached Philip Morris directly, "with no instigation," about a consulting position, because Abood "was tired of the infighting at CTR and thought that he would resign." Ahrensfeld's memorandum reported his discussion with Seligman that Ahrensfeld and Holtzman "were under instructions to preserve the integrity of the industry with respect to CTR . . . [and] it would be improper for us to give the impression that we had attempted to wean [Abood] away from CTR." Ahrensfeld outlined two positions that were acceptable to take in developing a relationship with Abood. One course was that if Abood voluntarily resigned his position with CTR, after passage of a reasonable period of time, Philip Morris could enter a consulting agreement with Abood. The second course was that if Abood voluntarily resigned and, before the passage of a reasonable period of time, Abood was approached by NIDA or another tobacco company, then Philip Morris could enter an agreement with Abood. [2015056747-6748, Cipollone privileged; dups 2015062701-2702; 2010070367-0368]

In August 1978, Abood informed Osdene that Abood had been visited by CTR representatives regarding "his future contract." Abood told CTR representatives that he wanted to terminate his work, and CTR asked him to submit a renewal proposal which it would then reject, "since the proposal will involve CNS work which is outside the guidelines set for the CTR program." Abood felt he could then start any new program in January 1979. [1000127935, not produced]

Abood's reference to new work in January evidently referred to a draft proposal under consideration by Philip Morris for sponsorship. Osdene suggested funding Abood in a combination of three ways: a grant, a consultancy, and a contract. [1001800009, Cipollone produced; dup 1000127930, not produced]

Osdene recommended a grant to Abood to continue his search for sites and mechanism action of nicotine in the brain. The first-year funding would be about $60,000 and would be largely unrestricted.

For his consultancy, Abood would be paid $300/day on an ad hoc basis for advice regarding Philip Morris' Nicotine Program, particularly in the area of Behavioral Psychology and Physiology.

Osdene recommended a contract with Abood to have him test specific compounds developed at Philip Morris and in which Philip Morris had a proprietary interest. The purpose of the contract was to "retain absolute control over the disposal of any data generated on these compounds."

In November 1978, Osdene informed Abood that he thought that his CTR contract would be renewed. Abood replied that he would "turn it down." [1000127934, not produced] A somewhat cryptic note written by Osdene a few days later reported a telephone conversation among Seligman, Osdene, and Ahrensfeld. Ahrensfeld said that, "he will go along with this as long as it's a bona fide deal." [1000127933, not produced] Osdene also recorded the decision: "Wait to contact Ed Jacob who is polling industry re support of Abood." [1000127933, not produced] No other documents clarified this note.

On December 7, 1978, Abood sent Philip Morris a revised proposal entitled, "Characterization of Brain Receptors for Nicotine and Nicotine-like Peptides Present in Brain." [1003289985-9989, Cipollone taken] On December 18, 1978, Osdene met with Abood and Philip Morris lawyer Carl Adkins in New York to discuss mechanisms of funding this proposal. It was decided to keep the proprietary areas within a contract or consultancy. The "synthetic work," i.e., the testing of Philip Morris synthesized compounds, would be done under contract. Osdene stated his preference to make a grant to Abood rather than a gift to the University of Rochester. Adkins stated, "Do not bring Univ[ersity] into grant." Abood felt it was "best to avoid rights under grant to Univ[ersity]." [1000127990, not produced]

In odd contrast to the discussion of December 18, a memorandum from Carl Adkins to Seligman on January 4, 1979, stated that the grant would be to the Center for Brain Research at the University of Rochester. Adkins reported that in the draft letter

to Abood accepting his research proposal, Adkins did not insist upon certain rights such as control of publication of results, absolute confidentiality, and exclusive use of any inventions or discoveries arising from the research. He stated that these rights would have to be negotiated with the University administration and that "in view of the small likelihood that anything of commercial value will result from this particular research," it was decided to avoid delay by undertaking more negotiations. [1005141428, not produced]

The December 7 proposal was accepted by Seligman in a letter to Abood on January 15, 1979. This letter outlined the terms for Abood's grant proposal. The Philip Morris funds would be used for no other purpose than for Abood's research described in his proposal and that all information obtained through the research would be available to Philip Morris. Furthermore, any information furnished by Philip Morris to Abood would be returned upon request. The letter also stipulated that Philip Morris had rights to any invention or discovery resulting from the research. [1000127877-7880, not produced]

In another letter on February 28, 1979, Seligman outlined Philip Morris' acceptance of Abood's grant and Philip Morris' intention to hire Abood as a consultant and as a contractor to test proprietary compounds. [1000127884, not produced]

3. Commercial Application

That Philip Morris recognized and was interested in the commercial application of Abood's work was clear from statements made in Osdene's August 1978 review of Abood's proposal and in Seligman's January 15, 1979, letter to Abood. Philip Morris went to considerable effort to ensure that Abood's work was controlled by the three mechanisms outlined above. It was determined that Abood had no NIDA funds for any of his work involving nicotine. [1001800009, Cipollone produced; dup 1000127930, not produced] Osdene also noted that the contract with Abood should allow Philip Morris to retain absolute control over the disposal of any data generated on experimental compounds.

After the first year of Abood's grant was completed, several Philip Morris scientists commented on the benefits that his program brought to Philip Morris. J.L. Charles, in a March 18, 1980 memorandum, stated his opinion that nicotine was a "powerful pharmacological agent" and had been cited as "'a reason for smoking.'" For these reasons:

> [O]ur ability to ascertain the structural features of the nicotine molecule which are responsible for its various pharmacological

properties can lead to the design of compounds with enhanced desirable properties (central nervous system effects) and minimized suspect properties (peripheral nervous system effects). There are many opportunities for acquiring proprietary compounds which can serve as a firm foundation for new and innovative products in the future. [1003289974-9975, Cipollone exhibit; dup 1000127793-7795, not produced]

Charles wrote that the receptor program at the University of Rochester was an integral part of the nicotine program at Philip Morris and could be justified in a number of ways. He wrote that the "combination of basic research on the pharmacology of the nicotine receptor combined with the capability to screen nicotine analogs for CNS activity complements our internal synthetic and behavioral efforts in the nicotine program." He felt the program was "justified in my view as a defensive response to the anti-smoking forces criticisms of nicotine and also as fundamental research into the nature of our product and how it affects our customers, the smokers." [1003289974-9975, Cipollone exhibit; dup 1000127793-7795, not produced]

In a March 21, 1980 memorandum, E.D. Sanders wrote that Abood's collaboration with Philip Morris was extremely beneficial and valuable. Abood's interaction with Philip Morris was crucial in establishing the prostration syndrome there. The Nicotine Program's goals were to determine whether the central and peripheral effects of nicotine could be "'separated'" and to design a nicotine analogue which would have nicotine-like activity in the CNS with little or no activity in the peripheral nervous system. The value of Abood's prostration syndrome test was the indication that nicotine did not appear to be mediated by a cholinergic receptor. Sanders believed that since nicotine's peripheral effects were well known to be cholinergic, the discovery of a non-cholinergic central receptor indicated the possibility of developing compounds meeting the above-stated goals. [1003289967-9968, Cipollone taken; dup 1000127786-7788, not produced]

Osdene, Seeman, and Dunn also commented on Abood's Nicotine Receptor Program at the University of Rochester. All felt that the project was of great benefit to Philip Morris. [1000127770-7771, not produced; dup 1003289965-9966, Cipollone exhibit; 1003289972-9973, Cipollone exhibit, all previous redactions highlighted; dup 1000127796-7798, not produced; 1000127789-7790, Cipollone privileged; dup 1003289969-9970, not produced]

4. Nicotine Binding to Rat Brain Membranes

On February 19, 1980, Abood sent Osdene a progress report covering the first year's research results from the period March 1979 to March 1980. The first year's work focused on several different areas including 1) isolation of pituitary peptides with neuroeffector actions; 2) identification of neuroactive peptides; 3) characterization of the muscarinic cholinergic receptor from mammalian brain; and 4) characterization of the opiate receptor from mammalian brain. [1000127582, Cipollone produced; 1000127583-7587, Cipollone taken]

On June 20, 1980, Osdene received a manuscript from Abood entitled, "Stereospecific ^{3}H-Nicotine Binding to Intact and Solubized Rat Brain Membranes and Evidence for Its Noncholinergic Nature." It acknowledged funding support from Philip Morris and USPH. A comparison was made of the ability of a variety of cholinergic drugs and nicotine derivatives to compete with ^{3}H-nicotine binding and their relative potency to produce or inhibit the prostration syndrome caused by nicotine. It was found that a number of nicotinic cholinergic agonists did not produce the prostration syndrome when administered intraventricularly and that nicotinic cholinergic antagonists could not reverse or block the prostration syndrome produced by nicotine. It was concluded that the sites for nicotine binding were noncholinergic in nature. [1000127740-7747, Cipollone produced]

On February 5, 1981, Abood submitted a progress report for the second year of his research covering the period March 1980 to March 1981. [1000127625, Cipollone taken] On October 20, 1980, J. Seeman wrote a memorandum summarizing the second year of Abood's research. During the second year of Abood's efforts, Abood continued to develop the nicotine prostration syndrome and re-tested some of the analogs previously examined. Because of this work the Philip Morris Behavioral Group made significant advancements using in-house developed modifications and refinements of the prostration syndrome test. Abood also tested nicotine analogs prepared at Philip Morris using several different tests, such as receptor binding, binding to glass fiber filters, rat blood pressure procedures, and the prostration syndrome. [1003060873-0874, Cipollone produced, all redactions removed]

Future work planned by Philip Morris in collaboration with Abood included quantitating nicotinic activity at various receptors using rat brain receptors and torpedo fish membrane receptors. The goal was to correlate binding data with *in vivo* tests such as the prostration syndrome and discrimination study.

More work was aimed at isolating nicotine receptors from a variety of preparations. The ultimate goal involved the isolation, identification and characterization of receptors. [1003060875-0876, Cipollone produced]

In 1981 and 1982, Abood sent several reports to Philip Morris concerning his research on locating nicotine receptors. [1000127552, not produced; 1000127553-7567, not produced] A 1981 report was entitled, "Relationship of Receptor Binding Affinity of ^{3}H-Nicotine to Rat Brain Membranes and Pharmacologic Efficacy to Molecular Configuration of Nicotine Analogues." Abood reported results of several analogues tested that not only had a high affinity to bind to brain membranes, but also demonstrated psychotropic activity as measured by the prostration syndrome. Other analogues had a high binding affinity, but no psychotropic activity. [1000127591-7605, Cipollone produced]

In 1982, Abood reported in several manuscripts that he had isolated a nicotine binding site. [1002973295-3300, not produced; 1005020598-3320, not produced; 1000128325-8346, not produced]

In March 1983, Abood reported progress made in isolating a purified nicotine receptor. [1000127485, not produced; 1000127486-7496, not produced]

In March 1984, Abood reported the progress made during the period January 1983 to April 1984. He succeeded in improving methods to obtain better yields of a more active form of purified nicotine receptor. He conducted more research on binding sites with ^{3}H-nicotine, and he developed the methodology necessary to research the specific binding sites for ^{3}H-arginine vasopressin in rat brain. [1002973383, not produced; 1002973384-3392, not produced]

Abood requested continued support for his research for the period April 1984 to April 1985. Philip Morris sent the University of Rochester $40,250 on March 7, 1984, to cover the first six months of the sixth year of Abood's grant. [1000127311-7312, not produced; 1000127459-7460, not produced] No evidence of further funding was found. It was possible that Abood's funding from Philip Morris ceased some time after Philip Morris terminated its Nicotine Program.

5. Acetaldehyde Transport

The following discussion concerns the 1982 collaboration of DeNoble and Abood. The research focused on the transport of acetaldehyde to the brain.

The first study addressed the following objectives:

(1) To determine whether acetaldehyde was able to cross the blood-brain barrier;

(2) To determine if there was a differential uptake of acetaldehyde by the brain through intravenous or intraarterial injections;

(3) To determine the ratio of acetaldehyde in blood compared to brain following intravenous or intraarterial injections; and

(4) To determine if there was a regional brain distribution of acetaldehyde.

The procedure involved injecting the rats with C^{14}-acetaldehyde into the bloodstream and taking blood samples from the heart and from three sections of the brain: the cortex, midbrain, and cerebellum. Brain tissue was also taken.

It was found that acetaldehyde readily crossed the blood-brain barrier and that the ratio of blood acetaldehyde to brain acetaldehyde was 10 to 1. The results indicated that the site of injection, whether intravenous or intraarterial, had no bearing on the uptake of acetaldehyde by the brain. Finally, it appeared that acetaldehyde was evenly distributed in the brain.

The second study conducted with Abood was performed to determine whether differential uptake of C^{14}-acetaldehyde occurred by nerve endings, myelin (sheath surrounding nerve cells), and mitochondria.

In this experiment, the rats were injected with C^{14}-acetaldehyde intravenously. Five minutes following the injection the rats were sacrificed and the brains analyzed for the localization of the acetaldehyde. The analysis revealed that most of the acetaldehyde was concentrated in the myelin and nerve endings, while a smaller amount was present in the mitochondria.

DeNoble felt that the results obtained thus far warranted additional research on acetaldehyde at both the behavioral and the CNS level. [820120, 1002973617-3619, Rothgeb produced; 10000128478-8481 (dup), Rothgeb produced; 820421, 1003060442, 1003060443-0503 (p. 0460-0463), Rothgeb produced]

B. Ohio State University (Berntson)

1. Overview

Gary G. Berntson was first funded by Philip Morris in 1972 when he was a post-doctoral student at Rockefeller University. In June 1974 Berntson moved to Ohio State University where he reestablished contact with Philip Morris. He received Philip Morris funding there from 1975 to 1981, and he served as a consultant to the Philip Morris Behavioral Research Program from 1977 through 1983.

Berntson's Philip Morris sponsored research followed a natural progression from his early work on nicotine and feline aggression to his later work on the effect of nicotine on learning and stress behaviors in humans. It did not appear that Philip Morris had any specific plan for Berntson's work in a particular commercial application or product; however, the director of the Behavioral Research Program, Dr. Dunn, viewed the work to be related to the general investigation concerning the benefits of smoking.

Berntson's funding ended after completion of his research in the 1980-81 academic year. There was no documentation why funding ceased. Philip Morris evidently found Berntson's consultancy to be valuable, and this arrangement continued throughout 1983. Again, no documentation was found why his consultancy lapsed; however, it should be noted that the lapse occurred around the same time that Philip Morris terminated DeNoble and the Nicotine Program.

2. Rockefeller University Research

As a post-doctoral student, Gary Berntson received Philip Morris funding beginning in 1972. His grant supported research on a central nicotinic receptor system antagonistic to the muscarinic receptor system, the latter being association with aggression and stalking behavior. [1003290213, Cipollone taken]

Berntson reported that in the cat, aggression and stalking behavior were caused by injections of a cholinergic agonist, and that this effect was muscarinic. Berntson attempted to determine whether there was a central nicotinic system that was antagonistic to the muscarinic system. [1003290202, Cipollone not produced]

3. Ohio State University Research

a. Aggression and Pain Threshold in Cats

In 1974, Berntson submitted a proposal entitled, "The effect of nicotine on excitatory and inhibitory processes in learned and unlearned behaviors." [1003286238-6267, Cipollone taken] Berntson planned to investigate the effect of systemic and brain injections of nicotine, arecoline (a muscarinic agonist, or enhancer), and saline on feline aggression. His results showed that nicotine reduced both predatory-like biting attack on rats and hissing behavior as compared to saline and arecoline. [1003286224, Cipollone taken] These findings demonstrated discrete behavioral effects of nicotine at doses paralleling those in human smokers. [1003287972-7975, Cipollone taken]

In 1976, Berntson submitted a proposal to examine the pain-reducing properties of nicotine. He planned to study whether the systemic administration of nicotine would raise the pain threshold in cats by differentially lowering the emotional response to painful stimuli without suppressing sensation. [1003286198-6203, Cipollone taken] Berntson found that nicotine suppressed aggression but did not affect sensitivity or thresholds to shock. [1003286146-6163, Cipollone taken]

In 1977, Berntson submitted a proposal to study the effects of nicotine on rage behavior. He planned to study the effects of nicotine on pain-induced aggression in cats and to examine the receptor basis of nicotine-induced suppression of aggression. [1003286131-6142, Cipollone taken] No further reference or report was found regarding Berntson's research on nicotine and feline aggressive behaviors.

b. Stress and Memory in Humans

Also in 1977, Berntson extended his studies to the effects of nicotine on humans. He hypothesized that nicotine could reduce the effects of stress, and he proposed monitoring autonomic variables to determine the effects of nicotine on stress-related disturbances in performance tasks. [1003286144, Cipollone taken] In 1979, Berntson reported that high nicotine reduced galvanic skin reaction to stress as compared to the no-smoking and low nicotine conditions. [1003286377-6382, Cipollone taken]

In studies on learning begun in 1978, Berntson reported that in humans, nicotine specifically facilitated memory and clearly reduced reaction time regardless of memory set size, but low doses of nicotine had no consistent effect. [1003286377-6382, Cipollone taken]

In his studies in 1979 using human subjects, Berntson demonstrated that nicotine aided recall of a series of memory set items. Response time was faster after the subject had smoked a high nicotine cigarette than under the no-smoking or low nicotine conditions. [1003286326-6330, Cipollone taken] Other studies indicated that nicotine could facilitate memory in initial tasks, but increased proactive inhibition of recall in subsequent similar tests. [1003286313-6320, Cipollone taken]

c. Pain Sensitivity in Rats

Also in October 1977, Berntson reported the results of studies on pain sensitivity in the rat. He reported that nicotine greatly reduced pain sensitivity in the rat as measured by the tail flick test and the hot-plate test. [1003286166; 1003286167, both Cipollone taken]

In 1978 Berntson proposed a study to examine nicotine induced analgesia in rats. He found that low doses of nicotine induced potent analgesia in rats when administered directly into specific locations in the brain. [1003286377-6382, Cipollone taken]

In 1979, Berntson proposed a study entitled "Analgesic and other behavioral effects of nicotine." [1003286498 not produced] Berntson proposed examining the central distribution of effective receptor loci for nicotine-induced analgesia in rats. [1003286365-6371, Cipollone taken] Berntson had proposed the idea that nicotine produced analgesic effects by releasing vasopressin; however, using rats unable to synthesis vasopressin, Berntson showed that nicotine was analgesic without vasopressin release. [1003286326-6330, Cipollone taken]

d. Learning in Rats

In 1980 Berntson submitted a proposal entitled, "Effects of nicotine on learning and memory." He proposed studies to determine whether nicotine's effects on animal learning were mediated via vasopressin release. [1003286355-6364, Cipollone taken] He concluded that both nicotine and vasopressin facilitated memory in rats. He found that nicotine facilitated memory only in animals with endogenous sources of vasopressin.

In 1981 Berntson submitted an untitled proposal to evaluate the effect of nicotine on stimulus sensitivity, response habituation and associative learning using the conditioned expectancy paradigm, which involved the repeated presentation of two paired stimuli. This proposal was not funded. [1003286341-6350, Cipollone taken]

e. Consultancy

Berntson became a consultant for Philip Morris in June 1977, and continued in this capacity through 1983. There was no documentation why Berntson's 1981 proposal was not funded; however, as late as January 24, 1983, Charles stated in a letter to Berntson his view that Berntson could provide valuable consulting input to Philip Morris programs. [1003156858 not produced]

C. Medical College of Virginia (Egle)

1. Overview

The Egle research began in 1981 and was terminated by Philip Morris in June 1984. Egle was hired to screen nicotine analogs for their effect on rat blood pressure, and then a decision would be made by Philip Morris whether or not additional work was required. Philip Morris documents indicated that Egle's research was intertwined with other nicotine analog research Philip Morris was conducting. Egle was not aware of the work conducted by DeNoble, Abood or INBIFO. He may or may not have understood that the compounds he was testing were nicotine analogs. Egle referred to the compounds in his reports by number codes.

The primary purpose of the screening work was to determine the effect and mode of action of nicotine and nicotine analogs on the cardiovascular system. Egle's research progressed from simple screening of the effect of nicotine analogs on rat blood pressure to more detailed research to determine how analogs caused a decrease in blood pressure. Philip Morris' objective was to find compounds with desirable central nervous system effects but with little or no peripheral nervous system effects. [1002973191-3194; 1002973189-3190; 1002973196-3197]

The documents did not explicitly outline the reasons why Egle's research was terminated. On June 5, 1984, Osdene sent a letter to Egle informing him that Philip Morris was terminating the project. [1002973277; 1003157366] The termination of the Egle project occurred at approximately the same time as the termination of the Nicotine Program.

Documents concerning Egle's research were not produced in Cipollone because the topic of peripheral nervous system effects of nicotine was considered nonresponsive.

2. Projects

a. Dose Response Curves

In 1981, Egle proposed to determine the effect of intravenously administered compounds on rat blood pressure. Of thirty-six nicotine analogs tested, seventeen caused an increase in blood pressure, fifteen caused a decrease in blood pressure and four caused either an increase or decrease depending on the dose administered. [1002973250-3276] Compound CR-1974 was the most potent compound in decreasing blood pressure. [1000128485-8498; 1002973119-3131; 1003060029-0042] Compound CR-1766A caused a decrease in blood pressure up to a dose of 10 mg/kg but at higher doses, caused an increase in blood pressure. Nicotine produced an increase in blood pressure in a dose-related manner. Phase two of this research consisted of comparing results of analogs previously tested in albino rats with results obtained from tests with hooded rats. However, no research reports on this study were found.

b. Autonomic Blocking Study

The third phase was designed to determine the mode of action of two nicotine analogs, CR-1766A and CR-1974 because in the screening work, both had caused a decrease in rat blood pressure. Autonomic receptor blocking agents and surgical procedures were used to elucidate the mode of action of these compounds. [1000128234-8262; 1002973221-3249; 1003060000-0028; 1003157591-7618; 1003176942-6969; 1003582109-2137; 1002973250-3276] The goal of the research was to determine the autonomic neural receptor type affected by nicotine and the two test compounds. The autonomic blocking study demonstrated that nicotine increased blood pressure by causing the release of epinephrine from the adrenal glands. Following the administration of atropine (a muscarinic blocker), nicotine caused an increased heart rate. The study revealed that compound CR-1766A had a biphasic effect because it affected several different receptor sites. At doses greater than 10 mg/kg, CR-1766A caused an increase in blood pressure by its effect on alpha receptors. At lower doses, CR-1766A caused a decrease in blood pressure by activation of muscarinic and beta-2 receptors. CR-1974 exerted a negative effect on blood pressure and heart rate. This was determined to be the result of stimulation of muscarinic receptors. CR-1974 also affected beta-2 receptors and appeared to have weak ganglionic properties.

c. Adrenalectomy and/or Vagotomy

The fourth phase of Egle's research determined how much of the effects of nicotine, CR-1766A and CR-1974 were exerted as a result of secretion of epinephrine and how much were exerted by stimulation of the vagus nerve. [1002973250-3276] The experiment

used alpha and beta autonomic blocking drugs and adrenalectomy and vagotomy. The increase in blood pressure normally caused by nicotine was greatly reduced by adrenalectomy. Following vagotomy, nicotine increased heart rate rather than decreased heart rate. After adrenalectomy, CR-1766A at all doses caused a decrease in blood pressure but after vagotomy, it produced an increase in blood pressure. After vagotomy, CR-1974 caused an increase in blood pressure instead of a decrease in blood pressure.

d. Acute Toxicity Study

An acute toxicity study revealed an intravenous LD50 of 1.5 mg/kg for nicotine and 95.1 mg/kg for CR-2289. [1002973133-3134] The toxicity symptoms were initial respiratory stimulation followed by increased labored breathing and respiratory arrest.

D. Foundation for Behavioral Research (Hutchinson)

1. Overview

Ronald Hutchinson's research association with Philip Morris began in December 1969. [1003291007-1008, Cipollone taken; 1000048553-8556, not produced] At that time, Philip Morris funded two studies on the relationship between (1) aggression and smoking and humans, and (2) aggression and nicotine in monkeys. In February 1971, Philip Morris funded two more studies which essentially expanded on the theme of the previous aggression and nicotine in monkeys study. [1003291030-1031, Cipollone taken; 1003291033-1045, Cipollone Exhibit]

Hutchinson's research appeared to be part of Philip Morris' general research plan to study the benefits of smoking. Hutchinson presented the results of his work at the St. Martin's conference, and his work was subsequently published in 1973 as Chapter 11, "Effects of Nicotine on Avoidance, Conditioned Suppression and Aggression Response Measures in Animals and Man," in Dunn's book, Smoking Behavior: Motives and Incentives. [1003292259-2296, Cipollone Exhibit; 1001840650-0675, not produced] Hutchinson stated that, "Our interest in aggression and emotional reaction is fundamentally directed to understanding human behavior." It was interesting to note that Hutchinson himself had reservations about making his research results public. In the cover letter of one of his proposals, Hutchinson wrote to Dunn that the "basic outline is now at hand for understanding the psychopharmacologic effects of cigarette smoking," and that this information "constitutes an extremely powerful position for Philip Morris relative to its competitors." This indicated Hutchinson's recognition that research results from studies of this type might have commercial applications for Philip Morris. He believed that

Philip Morris could realize large profits from some of the research presented at the St. Martin's conference and questioned Philip Morris for presenting results to its competitors.

In September 1972, Hutchinson submitted a proposal to Philip Morris to study the "Blood pressure reductant effects of nicotine;" however, this study was ultimately funded through CTR as Grant No. 883 in 1973. Hutchinson received another CTR grant, No. 1107 in January 1977 to study the "Effects of acute and chronic nicotine administration on aggression and blood pressure reactions in rats and humans." This study was renewed in January 1978. [1003291057, not produced; 10000255182, not produced; 10000255259-5260, not produced] [1000036624-6630, Cipollone taken] [1005045263-5279, Cipollone taken]

2. Projects

a. Aggression and Smoking in Humans

The first project Hutchinson conducted, between 1969-1970, was entitled, "Effects of Cigarette Smoking Interruption and Resumption on Aggressive Levels in Humans." Using jaw clenching as a measure of aggression, Hutchinson measured experimentally-induced aggression levels in subjects, smoking at will before and during the experimental sessions, and in subjects smoke-deprived before and during the sessions. [1003291126-1142, not produced] Results showed that heart rate and blood pressure decreased upon cessation of smoking, while jaw clenching increased, then decreased. Triceps muscle contractions also increased somewhat after cessation of smoking. [1000029300-9345, Cipollone produced]

b. Aggression and Nicotine in Monkeys

The second research study undertaken by Hutchinson in 1969-1970 was entitled, "Effects of Nicotine Upon Shock-Induced Aggression in Squirrel Monkeys." [1003291126-1142, not produced] This study explored the effects of various doses of nicotine on artificially-induced, hyper-aggressive biting attacks in squirrel monkeys. Hutchinson found that on control days, three of the four monkeys tested had "before shock" lever presses (orienting reaction), while one of the four monkeys had no "before shock" reaction. Nicotine administration produced a dose-dependent increase in pre-shock lever pressing (orienting) in those three animals, while simultaneously producing a dose-dependent decrease in post-shock biting in all animals. [1000029300-9345, Cipollone produced]

c. Chronic Effects of Nicotine on Attack Reaction in Monkeys

Hutchinson proposed two new research proposals for the period 1971-1972. The first experiment was entitled, "Effects of Chronic Administration and Withdrawal of Nicotine Upon Shock-Produced Attack and Orienting Reactions in the Squirrel Monkey." This study sought to discover whether nicotine administration produced alterations in attack biting and orienting (lever pressing) reactions as compared to chlorpromazine and amphetamine administration, and to determine the effect of termination of these compounds on these reactions. [1003291033-1045, Cipollone Exhibit] The results demonstrated that chlorpromazine, chlordiazepoxide, and nicotine shifted response tendencies toward more pre-shock motor (lever pressing) reactions, while amphetamine increased both the pre-shock motor (lever pressing) and the post-shock biting attack behavior at low doses. Morphine administration decreased both behaviors. Hutchinson also investigated the effect of abrupt termination of chronic nicotine intake. When nicotine was withdrawn, subjects showed temporary large increases in post-shock biting attack behavior. After the third post-drug session, attacks were back to pre-nicotine biting levels, but not as low as the level during nicotine intake.

d. Conditioned Suppression in Rats and Monkeys

The second study conducted in the 1971-1972 period was entitled, "Effect of Subcutaneous Nicotine Upon Conditioned Suppression in Rats and Squirrel Monkeys." This study tested the stress reducing properties of nicotine using the conditioned suppression method. Subjects were conditioned to lever press for food rewards on a variable-interval reinforcement schedule. Subsequent to establishing a consistent pattern of responses, a 30 second tone followed by a shock was delivered on an unpredictable seven minute variable-interval, response-independent schedule. When responding had become stable during saline control injections, the subjects were injected with different doses of nicotine. The effect on suppression of responding (lever pressing) during the tone stimulus relative to responding during the absence of tone was assessed.

The results showed that for monkeys, responding (lever pressing) previously suppressed during the tone stimulus was increased at lower nicotine doses, but reduced a higher doses. In rats, administration of nicotine reduced the suppression of responding (lever pressing) during the tone stimulus at both low and intermediate doses [1003291033-1045, Cipollone Exhibit; 1003292259-2296, Cipollone Exhibit; 1001840650-0675, not produced]

Hutchinson concluded from his research that for both humans and monkeys, nicotine produced a differential reduction in behavior patterns associated with aggression and hostility, and this effect was similar to that produced by tranquilizers. The same dose of nicotine that decreased aggression would also elevate orienting and anticipatory reactions, an effect characteristic of tranquilizers. Nicotine also reduced the suppression of behavior caused by contact with fear or anxiety-producing stimuli. Hutchinson concluded that termination of chronic nicotine ingestion caused temporary increases in aggression, hostility and irritability in both monkeys and man. The finding "seemed to support strongly the proposition that the intake of nicotine in a stressful or noxious environment will constitute a reinforcing event and the termination of such a practice will constitute a punishing or negatively reinforcing event."

E. Rockefeller University (Waldbillig)

1. Overview

Robert Waldbillig was funded by Philip Morris from 1974 through 1976 when he was a post-doctoral student at Rockefeller University. Waldbillig conducted research on the effect of nicotine on shock-induced aggression and natural predatory behaviors in rats.

In October 1977, Dunn criticized Waldbillig for not having provided written reports on his Philip Morris-supported research. Although it was never clearly stated, there was the implication that Waldbillig's financial support was withdrawn for this reason.

2. Projects

a. Nicotine-Inhibited Aggression

In 1974, Waldbillig proposed to test the hypothesis that nicotine inhibited aggression by mimicking the action of brain acetylcholine. He planned to elicit intraspecies aggression in rats using painful tail shock before and after activation of brain chemoreceptors by an injection of nicotine. Waldbillig's goal was to establish the location of nicotine's site of action. If nicotine was shown to inhibit aggression, and its site of action specified, then Waldbillig planned to inject the active site with curare, a drug known to block the activation of nicotine receptors. He hypothesized that the loss of the nicotine inhibitory influence would result in increased aggressiveness. [1003290195-0197, Cipollone taken]

Waldbillig reported that the threshold for pain-induced aggression was raised by nicotine, and that he was attempting to determine nicotine's site of action by the systemic administration

of various antagonists in conjunction with nicotine. [1000362772-2795, Cipollone produced]

b. Predatory Attack

Waldbillig proposed in 1974 to study the effect of nicotine on the spontaneous predation of rats on mice. The method was simply to record attack latency before and after injection of nicotine in control solutions.

Waldbillig reported that his results revealed a clear inhibition of predatory attack in natural attackers that was not due to generalized effects such as debilitation or sedation. Nicotine-induced blockade of attack was observed during many months of testing. Such stability of findings argued strongly against an interpretation of inhibition in terms of stimulus generalization decrement. [1003285967-5970, Cipollone taken] Further study showed that the suppression of predatory attack was due to nicotine's action in the brain and not in the periphery.

c. Depletion of Serotonin on Aggression

In 1977, Waldbillig proposed research on the depletion of the neurotransmitter serotonin on aggression. Preliminary findings had indicated that the depletion of serotonin increased predatory attack. Serotonin-depleted animals were also hyperactive and hyper-reactive. Waldbillig proposed studying whether intraperitoneal injections of nicotine could reduce this hyper-responsiveness to normal levels.

In 1980, Waldbillig published an article on his Philip Morris sponsored research entitled, "Suppressive Effects of Intraperitoneal and Intraventricular Injections of Nicotine on Muricide and Shock-Induced Attack on Conspecifics." He reported that intraperitoneal injections of nicotine suppressed mouse-killing by rats in a dose dependent manner. Hexamethonium, a peripheral nicotinic receptor blocker, did not inhibit the suppression of aggression by nicotine. Mecamylamine, a central nicotinic receptor blocking agent, however, did reduce the inhibition of attack produced by nicotine. Waldbillig stated that although a CNS effect seemed likely, the exact mechanism of nicotine suppressed attack behavior could not be determined.